



**Europäisches
Patentamt**

**European
Patent Office**

**Office européen
des brevets**

11 JUN 2004

REC'D 15 JUL 2004

WIPO

PCT

Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

03015583.2

**PRIORITY
DOCUMENT**
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

BEST AVAILABLE COPY



Anmeldung Nr:
Application no.: 03015583.2
Demande no:

Anmeldetag:
Date of filing: 11.07.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

MERCK PATENT GmbH
Frankfurter Strasse 250
64293 Darmstadt
ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Benzimidazole carboxamides

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s)
revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D235/00

Am Anmeldetag benannte Vertragsstaaten/Contracting states designated at date of
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI

11. Juli 2003

**Merck Patent Gesellschaft
mit beschränkter Haftung
64271 Darmstadt**

Benzimidazole carboxamides

11. Juli 2003

- 1 -

Benzimidazole carboxamides

The present invention relates to benzimidazole carboxamides, benzimidazole carboxamides as medicaments, benzimidazole carboxamides as inhibitors of raf-kinase, the use of benzimidazole carboxamides for the manufacture of a pharmaceutical, a method for producing a pharmaceutical composition containing said benzimidazole carboxamides, the pharmaceutical composition obtainable by said method and a method of treatment, comprising administering said pharmaceutical composition.

Protein phosphorylation is a fundamental process for the regulation of cellular functions. The coordinated action of both protein kinases and phosphatases controls the levels of phosphorylation and, hence, the activity of specific target proteins. One of the predominant roles of protein phosphorylation is in signal transduction, where extracellular signals are amplified and propagated by a cascade of protein phosphorylation and dephosphorylation events, e.g. in the p21^{ras}/raf pathway.

The p21^{ras} gene was discovered as an oncogene of the Harvey (rasH) and Kirsten (rasK) rat sarcoma viruses. In humans, characteristic mutations in the cellular ras gene (c-ras) have been associated with many different types of cancers. These mutant alleles, which render Ras constitutively active, have been shown to transform cells, such as the murine cell line NIH 3T3, in culture.

The p21^{ras} oncogene is a major contributor to the development and progression of human solid cancers and is mutated in 30 % of all human cancers (Bolton et al. (1994) Ann. Rep. Med. Chem., 29, 165-74; Bos. (1989) Cancer Res., 49, 4682-9). In its normal, unmutated form, the ras protein is a key element of the signal transduction cascade directed by

growth factor receptors in almost all tissues (Avruch et al. (1994) Trends Biochem. Sci., 19, 279-83).

5 Biochemically, ras is a guanine nucleotide binding protein, and cycling between a GTP-bound activated and a GDP-bound resting form is strictly controlled by ras endogenous GTPase activity and other regulatory proteins. The ras gene product binds to guanine triphosphate (GTP) and guanine diphosphate (GDP) and hydrolyzes GTP to GDP. It is the GTP-bound state of Ras that is active. In the ras mutants in cancer cells, the
10 endogenous GTPase activity is alleviated and, therefore, the protein delivers constitutive growth signals to downstream effectors such as the enzyme raf kinase. This leads to the cancerous growth of the cells which carry these mutants (Magnuson et al. (1994) Semin. Cancer Biol., 5, 247-53). The ras proto-oncogene requires a functionally intact c-raf1 proto-
15 oncogene in order to transduce growth and differentiation signals initiated by receptor and non-receptor tyrosine kinases in higher eukaryotes.

Activated Ras is necessary for the activation of the c-raf1 proto-oncogene, but the biochemical steps through which Ras activates the Raf-1 protein
20 (Ser/Thr) kinase are now well characterized. It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase signaling pathway by administration of deactivating antibodies to raf kinase or by co-expression of dominant negative raf kinase or dominant negative MEK (MAPKK), the substrate of raf kinase, leads to the reversion of transformed
25 cells to the normal growth phenotype see: Daum et al. (1994) Trends Biochem. Sci., 19, 474-80; Fridman et al. (1994) J Biol. Chem., 269, 30105-8. Kolch et al. (1991) Nature, 349, 426-28) and for review Weinstein-Oppenheim et al. Pharm. & Therap. (2000), 88, 229-279.

30 Similarly, inhibition of raf kinase (by antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human tumor types (Monia et al., Nat. Med. 1996, 2, 668-75).

- Raf serine- and threonine-specific protein kinases are cytosolic enzymes that stimulate cell growth in a variety of cell systems (Rapp, U.R., et al. (1988) in *The oncogene handbook*; T. Curran, E.P. Reddy, and A. Skalka (ed.) Elsevier Science Publishers; The Netherlands, pp. 213-253; Rapp, U.R., et al. (1988) *Cold Spring Harbor Sym. Quant. Biol.* 53:173-184; Rapp, U.R., et al. (1990) *Inv Curr. Top. Microbiol. Amunol. Potter and Melchers (eds), Berlin, Springer-Verlag* 166:129-139).
- Three isozymes have been characterized:
- c-Raf (Raf-1) (Bonner, T.I., et al. (1986) *Nucleic Acids Res.* 14:1009-1015). A-Raf (Beck, T.W., et al. (1987) *Nucleic Acids Res.* 15:595-609), and B-Raf (Qkawa, S., et al. (1998) *Mol. Cell. Biol.* 8:2651-2654; Sithanandam, G. et a. (1990) *Oncogene*:1775). These enzymes differ in their expression in various tissues. Raf-1 is expressed in all organs and in all cell lines that have been examined, and A- and B-Raf are expressed in urogenital and brain tissues, respectively (Storm, S.M. (1990) *Oncogene* 5:345-351).
- Raf genes are proto-oncogenes: they can initiate malignant transformation of cells when expressed in specifically altered forms. Genetic changes that lead to oncogenic activation generate a constitutively active protein kinase by removal or interference with an N-terminal negative regulatory domain of the protein (Heidecker, G., et al. (1990) *Mol. Cell. Biol.* 10:2503-2512; Rapp, U.R., et al. (1987) in *Oncogenes and cancer* S. A. Aaronson, J. Bishop, T. Sugimura, M. Terada, K. Toyoshima, and P. K. Vogt (ed). Japan Scientific Press, Tokyo). Microinjection into NIH 3T3 cells of oncogenically activated but not wild-type versions of the Raf-protein prepared with *Escherichia coli* expression vectors results in morphological transformation and stimulates DNA synthesis (Rapp, U.R., et al. (1987) in *Oncogenes and cancer*; S. A. Aaronson, J. Bishop, T. Sugimura, M.

- Terada, K. Toyoshima, and P. K. Vogt (ed.) Japan Scientific Press, Tokyo; Smith, M. R., et al (1990) Mol. Cell. Biol. 10:3828-3833). Activating mutants of B-Raf have been identified in a wide range of human cancers e.g. colon, ovarien, melanomas and sarcomas (Davies, H., et al. (2002),
5 Nature 417 949-945. Published online June 9, 2002, 10.1038/nature00766). The preponderant mutation is a single phosphomimetic substitution in the kinase activation domain (V599E), leading to constitutive kinase activity and transformation of NIH3T3 cells.
- 10 Thus, activated Raf-1 is an intracellular activator of cell growth. Raf-1 protein serine kinase in a candidate downstream effector of mitogen signal transduction, since Raf oncogenes overcome growth arrest resulting from a block of cellular ras activity due either to a cellular mutation (ras revertant cells) or microinjection of anti-ras antibodies (Rapp, U.R., et al. (1988) in
15 The Oncogene Handbook, T. Curran, E.P. Reddy, and A. Skalka (ed.), Elsevier Science Publishers; The Netherlands, pp. 213-253; Smith, M.R., et al. (1986) Nature (London) 320:540-543).
- c-Raf function is required for transformation by a variety of membrane-
20 bound oncogenes and for growth stimulation by mitogens contained in serums (Smith, M.R., et al. (1986) Nature (London) 320:540-543). Raf-1 protein serine kinase activity is regulated by mitogens via phosphorylation (Morrison, D.K., et al. (1989) Cell 58:648-657), which also effects sub cellular distribution (Olah, Z., et al. (1991) Exp. Brain Res. 84:403; Rapp,
25 U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184. Raf-1 activating growth factors include platelet-derived growth factor (PDGF) (Morrison, D.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859), colony-stimulating factor (Baccarini, M., et al. (1990) EMBO J. 9:3649-3657), insulin (Blackshear, P.J., et al. (1990) J. Biol. Chem. 265:12115-
30 12118), epidermal growth factor (EGF) (Morrison, R.K., et al. (1988) Proc. Natl. Acad. Sci. USA 85:8855-8859), interleukin 2 (Turner, B.C., et al (1991) Proc. Natl. Acad. Sci. USA 88:1227), and interleukin 3 and

granulocytemacrophage colony-stimulating factor (Carroll, M.P., et al (1990) J. Biol. Chem. 265:19812-19817).

5 Upon mitogen treatment of cells, the transiently activated Raf-1 protein serine kinase translocates to the perinuclear area and the nucleus (Olah, Z., et al. (1991) Exp. Brain Res. 84:403; Rapp, U.R., et al. (1988) Cold Spring Harbor Sym. Quant. Biol. 53:173-184). Cells containing activated Raf are altered in their pattern of gene expression (Heidecker, G., et al. (1989) in Genes and signal transduction in multistage carcinogenesis, N. Colburn (ed.), Marcel Dekker, Inc., New York, pp. 339-374), and Raf
10 oncogenes activate transcription from Ap-1/PEA3-dependent promoters in transient transfection assays (Jamal, S., et al (1990) Science 344:463-466; Kaibuchi, K., et al (1989) J. Biol. Chem. 264:20855-20858; Wasylyk, C., et al. (1989) Mol. Cell. Biol. 9:2247-2250).

15 There are at least two independent pathways for Raf-1 activation by extracellular mitogens: one involving protein kinase C (KC) and a second initiated by protein tyrosine kinases (Blackshear, P.J., et al. (1990) J. Biol. Chem. 265:12131-12134; Kovacina, K.S., et al (1990) J. Biol. Chem. 265:12115-12118; Morrison, D.K., et al. (1988) Proc. Natl. Acad. Sci. USA
20 85:8855-8859; Siegel, J.N., et al (1990) J. Biol. Chem. 265:18472-18480; Turner, B.C., et al (1991) Proc. Natl. Acad. Sci. USA 88:1227). In either case, activation involves Raf-1 protein phosphorylation. Raf-1 phosphorylation may be a consequence of a kinase cascade amplified by
25 autophosphorylation or may be caused entirely by autophosphorylation initiated by binding of a putative activating ligand to the Raf-1 regulatory domain, analogous to PKC activation by diacylglycerol (Nishizuka, Y. (1986) Science 233:305-312).

30 The process of angiogenesis is the development of new blood vessels, generally capillaries, from pre-existing vasculature. Angiogenesis is defined as involving (i) activation of endothelial cells; (ii) increased

5 vascular permeability; (iii) subsequent dissolution of the basement membrane and extravasation of plasma components leading to formation of a provisional fibrin gel extracellular matrix; (iv) proliferation and mobilization of endothelial cells; (v) reorganization of mobilized endothelial cells to form functional capillaries; (vi) capillary loop formation; and (vii) deposition of basement membrane and recruitment of perivascular cells to newly formed vessels.

10 Normal angiogenesis is activated during tissue growth, from embryonic development through maturity, and then enters a period of relative quiescence during adulthood.

15 Normal angiogenesis is also activated during wound healing, and at certain stages of the female reproductive cycle. Inappropriate or pathological angiogenesis has been associated with several disease states including various retinopathies; ischemic disease; atherosclerosis; chronic inflammatory disorders; rheumatoid arthritis, and cancer. The role of angiogenesis in disease states is discussed, for instance, in Fan et al, Trends in Pharmacol Sci. 16:54-66; Shawver et al, DOT Vol. 2, No. 2
20 February 1997; Folkmann, 1995, Nature Medicine 1:27-31.

25 In cancer the growth of solid tumors has been shown to be angiogenesis dependent. (See Folkmann, J., J. Nat'l. Cancer Inst., 1990, 82, 4-6.) Consequently, the targeting of pro-angiogenic pathways is a strategy being widely pursued in order to provide new therapeutics in these areas of great, unmet medical need.

30 Raf is involved in angiogenic processes. Endothelial growth factors (e.g. vascular endothelial growth factor VEGF) activates receptor tyrosine kinases (e.g. VEGFR-2) and signal through the Ras/Raf/Mek/Erk kinase cascade. Activation of VEGFR-2 by VEGF is a critical step in the signal

transduction pathway that initiates tumor angiogenesis. VEGF expression may be constitutive to tumor cells and can also be upregulated in response to certain stimuli. One such stimuli is hypoxia, where VEGF expression is upregulated in both tumor and associated host tissues. The VEGF ligand
5 activates VEGFR-2 by binding with its extracellular VEGF binding site. This leads to receptor dimerization of VEGFRs and autophosphorylation of tyrosine residues at the intracellular kinase domain of VEGFR- 2. The kinase domain operates to transfer a phosphate from ATP to the tyrosine residues, thus providing binding sites for signaling proteins downstream of
10 VEGFR-2 leading ultimately to initiation of angiogenesis (McMahon, G., The Oncologist, Vol. 5, No. 90001, 3-10, April 2000).

Mice with a targeted disruption in the Braf gene die of vascular defects during development (Wojnowski, L. et al. 1997, Nature genetics 16, page
15 293- 296). These mice show defects in the formation of the vascular system and in angiogenesis e.g. enlarged blood vessels and increased apoptotic death of differentiated endothelial cells.

For the identification of a signal transduction pathway and the detection of
20 cross talks with other signaling pathways suitable models or model systems have been generated by various scientists, for example cell culture models (e.g. Khwaja et al., EMBO, 1997, 16, 2783-93) and transgenic animal models (e.g. White et al., Oncogene, 2001, 20, 7064-7072). For the examination of particular steps in the signal transduction
25 cascade, interfering compounds can be used for signal modulation (e.g. Stephens et al., Biochemical J., 2000, 351, 95-105). The compounds according to the invention may also be useful as reagents for the examination of kinase dependent signal transduction pathways in animal and/or cell culture models or any of the clinical disorders listed throughout
30 this application.

5 The measurement of kinase activity is a well known technique feasible for each person skilled in the art. Generic test systems for kinase activity detection with substrates, for example histone (e.g. Alessi et al., FEBS Lett. 1996, 399, 3, page 333-8) or myelin basic protein are well described in the literature (e.g. Campos-González, R. and Glenney, Jr., J.R. 1992 *J. Biol. Chem.* 267, Page 14535).

10 For the identification of kinase inhibitors various assay systems are available (see for example Walters et al., *Nature Drug Discovery* 2003, 2; page 259-266). For example, in scintillation proximity assays (e.g. Sorg et al., *J. of. Biomolecular Screening*, 2002, 7, 11-19) or flashplate assays the radioactive phosphorylation of a protein or peptide as substrate with γ ATP can be measured. In the presence of an inhibitory compound no signal or a decreased radioactive signal is detectable. Furthermore homogeneous
15 time-resolved fluorescence resonance energy transfer (HTR-FRET), and fluorescence polarization (FP) technologies are useful for assay methods (for example Sills et al., *J. of Biomolecular Screening*, 2002, 191-214).

20 Other non-radioactive ELISA based assay methods use specific phospho-antibodies (AB). The phospho-AB binds only the phosphorylated substrate. This binding is detectable with a secondary peroxidase conjugated antibody, measured for example by chemiluminescence (for exaple Ross et al., *Biochem. J.*, 2002, 366, 977-981).

25 The present invention provides compounds generally described as benzimidazole carboxamides, including both aryl and/or heteroaryl derivatives, which are preferably kinase inhibitors and more preferably inhibitors of the enzyme raf kinase. Since the enzyme is a downstream effector of p21^{ras}, the inhibitors are useful in pharmaceutical compositions
30 for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth

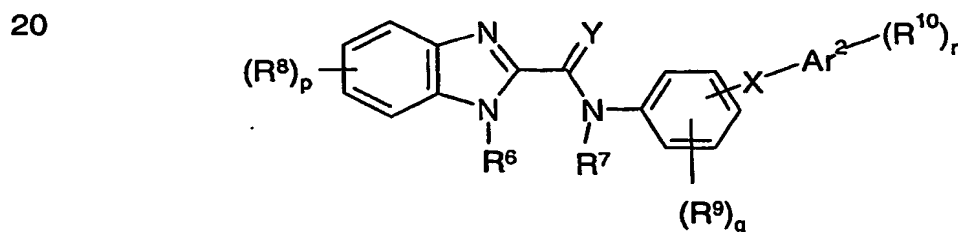
mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal solid cancers, e.g. murine cancer, since the progression of these cancers is dependent upon the ras protein signal transduction cascade and therefore susceptible to treatment by

5 interruption of the cascade, i.e., by inhibiting raf kinase. Accordingly, the compound of Formula I or a pharmaceutically acceptable salt thereof is administered for the treatment of diseases mediated by the raf kinase pathway especially cancers, including solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon),

10 myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma), pathological angiogenesis and metastatic cell migration. Furthermore the compounds are useful in the treatment of complement activation dependent chronic inflammation (Niculescu et al. (2002) Immunol. Res., 24:191-199) and HIV-1 (human immunodeficiency virus

15 type1) induced immunodeficiency (Popik et al. (1998) J Virol, 72: 6406-6413).

Therefore, subject of the present invention are compounds of formula I



25
wherein

R^6, R^7 are independently from one another H, A or SO_2A ,

30 A is independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylencycloalkyl, alkoxy and alkoxyalkyl,

- R^8, R^9 and R^{10} are independently selected from a group consisting of
 H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal,
 CH_2Hal , $CH(Hal)_2$, $C(Hal)_3$, NO_2 , $(CH_2)_nCN$,
 5 $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nOR^{11}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$,
 $(CH_2)_nCOOR^{12}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$,
 $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$,
 $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$,
 $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $CH=N-OA$, $CH_2CH=N-OA$,
 10 $(CH_2)_nNHOA$, $(CH_2)_nCH=N-R^{11}$, $(CH_2)_nOC(O)NR^{11}R^{12}$,
 $(CH_2)_nNR^{11}COOR^{12}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$,
 $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$,
 $(CH_2)_nN(R^{11})C(R^{13})HCOOR^{12}$, $C(R^{13})HCOOR^{12}$,
 $(CH_2)_nN(R^{11})CH_2CH_2N(R^{12})CH_2COOR^{12}$,
 15 $(CH_2)_nN(R^{11})CH_2CH_2NR^{11}R^{12}$, $CH=CHCOOR^{11}$,
 $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2NR^{11}R^{12}$,
 $CH=CHCH_2OR^{13}$, $(CH_2)_nN(COOR^{11})COOR^{12}$,
 $(CH_2)_nN(CONH_2)COOR^{11}$, $(CH_2)_nN(CONH_2)CONH_2$,
 $(CH_2)_nN(CH_2COOR^{11})COOR^{12}$,
 20 $(CH_2)_nN(CH_2CONH_2)COOR^{11}$,
 $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{11}$,
 $(CH_2)_nCHR^{13}COOR^{11}$, $(CH_2)_nCHR^{13}CH_2OR^{14}$,
 $(CH_2)_nOCN$ and $(CH_2)_nNCO$, wherein
- 25 R^{11}, R^{12} are independently selected from a group consisting of
 H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$, or in $NR^{11}R^{12}$,
- R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-,
 6- or 7-membered heterocyclous which optionally
 30 contains 1 or 2 additional hetero atoms, selected from
 N, O and S,

	R^{13}, R^{14}	are independently selected from a group consisting of H, Hal, A, $(CH_2)_mAr^4$ and $(CH_2)_mHet$,
5	Ar^3, Ar^4	are independently from one another aromatic hydrocarbon residues comprising 5 to 12 and preferably 5 to 10 carbon atoms which are optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15} , $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,
10		
	Het	is a saturated, unsaturated or aromatic heterocyclic residue which is optionally substituted by one or more substituents, selected from a group consisting of A, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$, $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$, COR^{15} , $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,
15		
	R^{15}, R^{16}	are independently selected from a group consisting of H, A, and $(CH_2)_mAr^6$, wherein
20		
	Ar^6	is a 5- or 6-membered aromatic hydrocarbon which is optionally substituted by one or more substituents selected from a group consisting of methyl, ethyl, propyl, 2-propyl, tert.-butyl, Hal, CN, OH, NH_2 and CF_3 ,
25		
	k, m and n	are independently of one another 0, 1, 2, 3, 4, or 5,
	X	represents a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h-Q-(CHR^{12})_l$, wherein
30		

- Q is selected from a group consisting of O, S, N-R¹⁵, (CHal₂)_j, (O-CHR¹⁸)_j, (CHR¹⁸-O)_j, CR¹⁸=CR¹⁹, (O-CHR¹⁸CHR¹⁹)_j, (CHR¹⁸CHR¹⁹-O)_j, C=O, C=S, C=NR¹⁵, CH(OR¹⁵), C(OR¹⁵)(OR²⁰), C(=O)O, OC(=O), OC(=O)O, C(=O)N(R¹⁵), N(R¹⁵)C(=O), OC(=O)N(R¹⁵), N(R¹⁵)C(=O)O, CH=N-O, CH=N-NR¹⁵, S=O, SO₂, SO₂NR¹⁵ and NR¹⁵SO₂, wherein
- 5
- R¹⁸, R¹⁹, R²⁰ are independently selected from the meanings given for R⁸, R⁹ and R¹⁰, preferably independently selected from the group consisting of H, A, Hal, CH₂Hal, CH(Hal)₂, C(Hal)₃, NO₂, (CH₂)_nCN, (CH₂)_nOR¹¹, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nNR¹¹COR¹³, (CH₂)_nNR¹¹CONR¹¹R¹², (CH₂)_nNR¹¹SO₂A, (CH₂)_nSO₂NR¹¹R¹², (CH₂)_nS(O)_uR¹³, (CH₂)_nCOR¹³, (CH₂)_nSR¹¹, (CH₂)_nNHOA and (CH₂)_nNR¹¹COOR¹³,
- 10
- 15
- h, i are independently from each other 0, 1, 2, 3, 4, 5, or 6, and
- 20
- j is 1, 2, 3, 4, 5, or 6,
- Y is selected from O, S, NR²¹, C(R²²)-NO₂, C(R²²)-CN and C(CN)₂, wherein
- 25
- R²¹ is independently selected from the meanings given for R¹³, R¹⁴ and
- 30
- R²² is independently selected from the meanings given for R¹¹, R¹²,

- 13 -

- p, r are independently from one another 0, 1, 2, 3, 4 or 5,
- q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,
- 5 u is 0, 1, 2 or 3, preferably 0, 1 or 2,
- and
- 10 Hal is independently selected from a group consisting of F, Cl, Br and I;
- and the salts and solvates thereof, preferably the physiologically acceptable salts and solvates thereof.
- 15 Even more preferred are compounds of formula I
- wherein
- 20 Ar^2 is selected from aromatic hydrocarbons containing 6 to 10 and especially 6 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 8 and especially 4 to 6 carbon atoms and one or two heteroatoms, independently selected from N, O and S and especially selected from N and O,
- 25 R^8 , R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl 3 to 7 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, $C(Hal)_3$, NO_2 , $(CH_2)_nCN$, $(CH_2)_nOR^{11}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$,
- 30

- 14 -

- $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $(CH_2)_nNHOA$,
 $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$,
 $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$,
 $(CH_2)_nN(R^{11})C(R^{13})HCOOR^8$, $(CH_2)_nN(R^{11})$,
 $C(R^{13})HCOOR^8$, $(CH_2)_nN(COOR^{13})COOR^{14}$,
 $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$,
 $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$,
 $(CH_2)_nN(CH_2CONH_2)COOR^{13}$,
 $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$,
 $(CH_2)_nCHR^{13}COOR^{14}$ and $(CH_2)_nCHR^{13}CH_2OR^{14}$,
- X represents a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h-Q-(CHR^{12})_i$, wherein
- Q is selected from a group consisting of O, S, $N-R^{15}$, $(CHAl_2)_j$, $(O-CHR^{18})_j$, $(CHR^{18}-O)_j$, $CR^{18}=CR^{19}$, $(O-CHR^{18}CHR^{19})_j$, $(CHR^{18}CHR^{19}-O)_j$, $C=O$, $C=NR^{15}$, $CH(OR^{15})$, $C(OR^{15})(OR^{20})$, $C(=O)N(R^{15})$, $N(R^{15})C(=O)$, $CH=N-NR^{15}$, $S=O$, SO_2 , SO_2NR^{15} and $NR^{15}SO_2$, wherein
- h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6, preferably 0, 1, 2 or 3 and
- j is 1, 2, 3, 4, 5 or 6, preferably 1, 2, 3 or 4,
- p is 1, 2, 3 or 4, preferably 1, 2 or 3, and
- r is 0, 1, 2, or 3, preferably 0, 1 or 2;
- and the salts and solvates thereof, preferably the physiologically acceptable salts and solvates thereof.

As used herein, the term "effective amount" means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

As used herein, the term "alkyl" preferably refers to a straight or branched chain hydrocarbon having from one to twelve carbon atoms, optionally substituted with substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylsulfanyl, C₁-C₆ alkylsulfenyl, C₁-C₆ alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or C₁-C₆ perfluoroalkyl, multiple degrees of substitution being allowed. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, and the like.

As used herein, the term "alkylene" preferably refers to a straight or branched chain divalent hydrocarbon radical having from one to ten carbon atoms, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl, optionally substituted by alkyl, nitro, cyano, halogen and lower perfluoroalkyl, multiple degrees of substitution being allowed.

Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, n-propylene, n-butylene and the like.

5 As used herein, the term "halogen" or "hal" preferably refers to fluorine (F), chlorine (Cl), bromine (Br) or iodine (I).

10 As used herein, the term "haloalkyl" preferably refers to an alkyl group as defined above, preferably containing at least 1 and at most 6 carbon atoms, substituted with at least one halogen, halogen being as defined herein. Examples of branched or straight chained "haloalkyl" groups useful in the present invention include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl and n-butyl substituted independently with one or more halogens, e.g., fluoro, chloro, bromo and iodo.

15 As used herein, the term "cycloalkyl" preferably refers to a non-aromatic cyclic hydrocarbon ring, preferably having from three to seven carbon atoms, which optionally includes an alkyl linker, preferably a C₁-C₆ alkyl linker, through which it may be attached. The alkyl or C₁-C₆ alkyl group is as defined above. Exemplary "cycloalkyl" groups include, but are not
20 limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein, the term "cycloalkylene" preferably refers to a non-aromatic alicyclic divalent hydrocarbon radical, preferably having from three to seven carbon atoms, which is optionally substituted with
25 substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, multiple
30 degrees of substitution being allowed. Examples of "cycloalkylene" as used herein include, but are not limited to, cyclopropyl-1,1-diyl,

cyclopropyl-1,2-diyl, cyclobutyl-1,2-diyl, cyclopentyl-1,3-diyl, cyclohexyl-1,4-diyl, cycloheptyl-1,4-diyl, or cyclooctyl-1,5-diyl, and the like.

As used herein, the term "heterocyclic" or the term "heterocyclyl"
5 preferably refers to a three to twelve-membered heterocyclic ring having one or more degrees of unsaturation containing one or more heteroatomic substitutions selected from S, SO, SO₂, O or N, optionally substituted with substituents selected from the group consisting of alkyl, haloalkyl, alkoxy, alkylsulfanyl, haloalkylsulfanyl, alkylsulfenyl, alkylsulfonyl, oxo, hydroxy,
10 mercapto, amino optionally substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, or perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more other "heterocyclic" ring(s) or cycloalkyl ring(s). Examples of "heterocyclic"
15 moieties include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, pyrrolidine, piperidine, morpholine, tetrahydrothiopyran, tetrahydrothiophene, and the like.

As used herein, the term "heterocyclylene" preferably refers to a three to
20 twelve-membered heterocyclic ring diradical having one or more degrees of unsaturation containing one or more heteroatoms selected from S, SO, SO₂, O or N, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally
25 substituted by alkyl, carboxy, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, nitro, cyano, halogen, lower perfluoroalkyl, multiple degrees of substitution being allowed. Such a ring may be optionally fused to one or more benzene rings or to one or more of another "heterocyclic" rings or cycloalkyl rings. Examples of
30 "heterocyclylene" include, but are not limited to, tetrahydrofuran-2,5-diyl, morpholine-2,3-diyl, pyran-2,4-diyl, 1,4-dioxane-2,3-diyl, 1,3-dioxane-

2,4-diyl, piperidine-2,4-diyl, piperidine-1,4-diyl, pyrrolidine-1,3-diyl, morpholine-2,4-diyl, and the like.

As used herein, the term "aryl" preferably refers to an optionally substituted benzene ring or to an optionally substituted benzene ring system fused to one or more optionally substituted benzene rings to form, for example, anthracene, phenanthrene, or naphthalene ring systems. Exemplary optional substituents include alkyl, alkoxy, alkylsulfanyl, alkylsulfenyl, alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. Examples of "aryl" groups include, but are not limited to Phenyl, 2-naphthyl, 1-naphthyl, biphenyl, as well as substituted derivatives thereof.

As used herein, the term "arylene" preferably refers to a benzene ring diradical or to a benzene ring system diradical fused to one or more optionally substituted benzene rings, optionally substituted with substituents selected from the group which includes lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl and aryl, multiple degrees of substitution being allowed. Examples of "arylene" include, but are not limited to benzene-1,4-diyl, naphthalene-1,8-diyl, anthracene-1,4-diyl, and the like.

As used herein, the term "aralkyl" preferably refers to an aryl or heteroaryl group, as defined herein, attached through a alkyl linker, wherein alkyl is as defined herein. Examples of "aralkyl" include, but are not limited to,

benzyl, phenylpropyl, 2-pyridylmethyl, 3-isoxazolylmethyl, 5-methyl-3-isoxazolylmethyl and 2-imidazolylethyl.

As used herein, the term "heteroaryl" preferably refers to a monocyclic five to seven-membered aromatic ring, or to a fused bicyclic aromatic ring system comprising two of such monocyclic five to seven-membered aromatic rings. These heteroaryl rings contain one or more nitrogen, sulfur and/or oxygen heteroatoms, where N-Oxides and sulfur Oxides and dioxides are permissible heteroatom substitutions and may be optionally substituted with up to three members selected from a group consisting of alkyl, haloalkyl, alkoxy, alkylsulfanyl, haloalkylsulfanyl, alkylsulfenyl, alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy, heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, perfluoroalkyl, heteroaryl or aryl, multiple degrees of substitution being allowed. Examples of "heteroaryl" groups used herein include furanyl, thiophenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, oxo-pyridyl, thiadiazolyl, isothiazolyl, pyridyl, pyridazyl, pyrazinyl, pyrimidyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothiophenyl, indolyl, indazolyl, and substituted versions thereof.

As used herein, the term "heteroarylene" preferably refers to a five to seven-membered aromatic ring diradical, or to a polycyclic heterocyclic aromatic ring diradical, containing one or more nitrogen, oxygen, or sulfur heteroatoms, where N-Oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions, optionally substituted with substituents selected from the group consisting of lower alkyl, lower alkoxy, lower alkylsulfanyl, lower alkylsulfenyl, lower alkylsulfonyl, oxo, hydroxy, mercapto, amino optionally substituted by alkyl, carboxy, tetrazolyl, carbamoyl optionally substituted by alkyl, aminosulfonyl optionally substituted by alkyl, acyl, aroyl, heteroaroyl, acyloxy, aroyloxy,

heteroaroyloxy, alkoxycarbonyl, nitro, cyano, halogen, lower perfluoroalkyl, heteroaryl, or aryl, multiple degrees of substitution being allowed. For polycyclic aromatic ring system diradicals, one or more of the rings may contain one or more heteroatoms. Examples of "heteroarylene" used
5 herein are furan-2,5-diyl, thiophene-2,4-diyl, 1,3,4-oxadiazole-2,5-diyl, 1,3,4-thiadiazole-2,5-diyl, 1,3-thiazole-2,5-diyl, pyridine-2,4-diyl, pyridine-2,3-diyl, pyridine-2,5-diyl, pyrimidine-2,4-diyl, quinoline-2,3-diyl, and the like.

10 As used herein, the term "alkoxy" preferably refers to the group R_aO- , where R_a is alkyl as defined above and the term "alkoxy" preferably refers to an alkoxy group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms. Exemplary alkoxy groups useful in the present invention include, but are not limited to methoxy, ethoxy, n-
15 propoxy, isopropoxy, n-butoxy and t-butoxy.

As used herein, the term "haloalkoxy" preferably refers to the group R_aO- , where R_a is haloalkyl as defined above and the term "haloalkoxy" preferably refers to an haloalkoxy group as defined herein wherein the
20 haloalkyl moiety contains at least 1 and at most 6 carbon atoms. Exemplary haloalkoxy groups useful in the present invention include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy and t-butoxy substituted with one or more halo groups, for instance trifluoromethoxy.

25 As used herein the term "aralkoxy" preferably refers to the group $R_C R_B O-$, where R_B is alkyl and R_C is aryl as defined above.

As used herein the term "aryloxy" preferably refers to the group $R_C O-$,
30 where R_C is aryl as defined above.

As used herein, the term "alkylsulfanyl" preferably refers to the group $R_A S-$, where R_A is alkyl as defined above and the term "alkylsulfanyl" preferably refers to an alkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

5

As used herein, the term "haloalkylsulfanyl" preferably refers to the group $R_D S-$, where R_D is haloalkyl as defined above and the term "haloalkylsulfanyl" preferably refers to a haloalkylsulfanyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

10

As used herein, the term "alkylsulfenyl" preferably refers to the group $R_A S(O)-$, where R_A is alkyl as defined above and the term "alkylsulfenyl" preferably refers to an alkylsulfenyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

15

As used herein, the term "alkylsulfonyl" preferably refers to the group $R_A SO_2-$, where R_A is alkyl as defined above and the term "alkylsulfonyl" preferably refers to an alkylsulfonyl group as defined herein wherein the alkyl moiety contains at least 1 and at most 6 carbon atoms.

20

As used herein, the term "oxo" preferably refers to the group $=O$.

As used herein, the term "mercapto" preferably refers to the group $-SH$.

25

As used herein, the term "carboxy" preferably refers to the group $-COOH$.

As used herein, the term "cyano" preferably refers to the group $-CN$.

30

As used herein, the term "cyanoalkyl" preferably refers to the group $-R_B CN$, wherein R_B is alkyl as defined above. Exemplary "cyanoalkyl"

groups useful in the present invention include, but are not limited to, cyanomethyl, cyanoethyl and cyanoisopropyl.

5 As used herein, the term "aminosulfonyl" preferably refers to the group -SO₂NH₂.

As used herein, the term "carbamoyl" preferably refers to the group -C(O)NH₂.

10 As used herein, the term "sulfanyl" shall refer to the group -S-.

As used herein, the term "sulfenyl" shall refer to the group -S(O)-.

15 As used herein, the term "sulfonyl" shall refer to the group -S(O)₂- or -SO₂-.

As used herein, the term "acyl" preferably refers to the group R_FC(O)-, where R_F is alkyl, cycloalkyl or heterocyclyl as defined herein.

20 As used herein, the term "aroyl" preferably refers to the group R_CC(O)-, where R_C is aryl as defined herein.

As used herein, the term "heteroaroyl" preferably refers to the group R_EC(O)-, where R_E is heteroaryl as defined herein.

25

As used herein, the term "alkoxycarbonyl" preferably refers to the group R_AOC(O)-, where R_A is alkyl as defined herein.

30 As used herein, the term "acyloxy" preferably refers to the group R_FC(O)O-, where R_F is alkyl, cycloalkyl, or heterocyclyl as defined herein.

As used herein, the term "aroxyloxy" preferably refers to the group $R_C C(O)O-$, where R_C is aryl as defined herein.

5 As used herein, the term "heteroaroxyloxy" preferably refers to the group $R_E C(O)O-$, where R_E is heteroaryl as defined herein.

As used herein, the term "carbonyl" or "carbonyl moiety" preferably refers to the group $C=O$.

10 As used herein, the term "thiocarbonyl" or "thiocarbonyl moiety" preferably refers to the group $C=S$.

As used herein, the term "amino", "amino group" or "amino moiety" preferably refers to the group $NR_G R_{G'}$, wherein R_G and $R_{G'}$ are preferably
15 selected, independently from one another, from the group consisting of hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, alkylencycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If both R_G and $R_{G'}$ are hydrogen, $NR_G R_{G'}$ is also referred to as "unsubstituted amino moiety" or "unsubstituted amino group". If R_G and/or $R_{G'}$ are other than hydrogen,
20 $NR_G R_{G'}$ is also referred to as "substituted amino moiety" or "substituted amino group".

As used herein, the term "imino" or "imino moiety" preferably refers to the group $C=NR_G$, wherein R_G is preferably selected from the group consisting
25 of hydrogen, alkyl, haloalkyl, alkenyl, cycloalkyl, alkylencycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If R_G is hydrogen, $C=NR_G$ is also referred to as "unsubstituted imino moiety". If R_G is a residue other than hydrogen, $C=NR_G$ is also referred to as "substituted imino moiety".

30

As used herein, the term "ethene-1,1-diyl moiety" preferably refers to the group $C=CR_K R_L$, wherein R_K and R_L are preferably selected, independently

from one another, from the group consisting of hydrogen, halogen, cyano, alkyl, haloalkyl, alkenyl, cycloalkyl, nitro, alkylencycloalkyl, cyanoalkyl, aryl, aralkyl, heteroaryl, acyl and aroyl. If both hydrogen R_K and R_L are hydrogen, $C=CR_KR_L$ is also referred to as "unsubstituted ethene-1,1-diyl moiety". If one of R_K and R_L or both are a residue other than hydrogen, $C=CR_KR_L$ is also referred to as "substituted ethene-1,1-diyl moiety".

As used herein, the terms "group", "residue" and "radical" or "groups", "residues" and "radicals" are usually used as synonyms, respectively, as it is common practice in the art.

As used herein, the term "optionally" means that the subsequently described event(s) may or may not occur, and includes both event(s), which occur, and events that do not occur.

As used herein, the term "physiologically functional derivative" preferably refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example, an ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

As used herein, the term "solvate" preferably refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula I or formula II or a salt or physiologically functional derivative thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic

acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

5

As used herein, the term "substituted" preferably refers to substitution with the named substituent or substituents, multiple degrees of substitution being allowed unless otherwise stated.

10 Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two or more stereoisomers, which are usually enantiomers and/or diastereomers. Accordingly, the compounds of this invention include mixtures of stereoisomers, especially mixtures of enantiomers, as well as purified
15 stereoisomers, especially purified enantiomers, or stereoisomerically enriched mixtures, especially enantiomerically enriched mixtures. Also included within the scope of the invention are the individual isomers of the compounds represented by formulae I and II above as well as any wholly or partially equilibrated mixtures thereof. The present invention also covers
20 the individual isomers of the compounds represented by the formulas above as mixtures with isomers thereof in which one or more chiral Centers are inverted. Also, it is understood that all tautomers and mixtures of tautomers of the compounds of formula I are included within the scope of the compounds of formula I and preferably the formulae and
25 subformulae corresponding thereto.

Racemates obtained can be resolved into the isomers mechanically or chemically by methods known per se. Diastereomers are preferably formed from the racemic mixture by reaction with an optically active
30 resolving agent. Examples of suitable resolving agents are optically active acids, such as the D and L forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid or the various

5 optically active camphorsulfonic acids, such as β -camphorsulfonic acid. Also advantageous is enantiomer resolution with the aid of a column filled with an optically active resolving agent (for example dinitrobenzoylphenylglycine); an example of a suitable eluent is a hexane/isopropanol/ acetonitrile mixture.

10 The diastereomer resolution can also be carried out by standard purification processes, such as, for example, chromatography or fractional crystallization.

It is of course also possible to obtain optically active compounds of the formula I or II by the methods described above by using starting materials which are already optically active.

15 Unless indicated otherwise, it is to be understood that reference to the compounds of formula I preferably includes the reference to the sub formulae corresponding thereto, for example the sub formulae I.1 to I.18 and preferably formulae Ia to Id. It is also understood that the following embodiments, including uses and compositions, although recited with
20 respect to formula I are preferably also applicable to sub formulae I.1 to I.18 and preferably formulae Ia to Id.

25 Subject of the present invention are especially compounds of formula I in which one or more substituents or groups, preferably the major part of the substituents or groups has a meaning which is indicated as preferred, more preferred, even more preferred or especially preferred.

30 In compounds of formula I, the term alkyl more preferably refers to an unbranched or branched alkyl residue, preferably an unbranched alkyl residue comprising 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, preferably 1, 2, 3, 4, 5 or 6, more preferred 1, 2, 3 or 4 and especially 1 or 2 carbon atoms, or a

branched alkyl residue comprising 3, 4, 5, 6, 7, 8, 9 or 10, preferably 3, 4, 5 or 6 more preferred 3 or 4 carbon atoms. The alkyl residues can be optionally substituted, especially by one or more halogen atoms, for example up to perhaloalkyl, by one or more hydroxy groups or by one or more amino groups, all of which can optionally be substituted by alkyl. If an alkyl residue is substituted by halogen, it usually comprises 1, 2, 3, 4 or 5 halogen atoms, depending on the number of carbon atoms of the alkyl residue. For example, a methyl group can comprise, 1, 2 or 3 halogen atoms, an ethyl group (an alkyl residue comprising 2 carbon atoms) can comprise 1, 2, 3, 4 or 5 halogen atoms. If an alkyl residue is substituted by hydroxy groups, it usually comprises one or two, preferably one hydroxy groups. If the hydroxy group is substituted by alkyl, the alkyl substituent comprises preferably 1 to 4 carbon atoms and is preferably unsubstituted or substituted by halogen and more preferred unsubstituted. If an alkyl residue is substituted by amino groups, it usually comprises one or two, preferably one amino groups. If the amino group is substituted by alkyl, the alkyl substituent comprises preferably 1 to 4 carbon atoms and is preferably unsubstituted or substituted by halogen and more preferred unsubstituted. According to compounds of formula I, alkyl is preferably selected from the group consisting of methyl, ethyl, trifluoro methyl, pentafluoro ethyl, isopropyl, tert.-butyl, 2-amino ethyl, N-methyl-2-amino ethyl, N,N-dimethyl-2-amino ethyl, N-ethyl-2-amino ethyl, N,N-diethyl-2-amino ethyl, 2-hydroxy ethyl, 2-methoxy ethyl and 2-ethoxy ethyl, further preferred of the group consisting of 2-butyl, n-pentyl, neo-pentyl, isopentyl, hexyl and n-decyl, more preferred of methyl, ethyl, trifluoro methyl, isopropyl and tert.-butyl.

In compounds of formula I, alkenyl is more preferably selected from the group consisting of allyl, 2- or 3-butenyl, isobutenyl, sec-butenyl, furthermore preferably 4-pentenyl, isopentenyl and 5-hexenyl.

In compounds of formula I, alkylene is more preferably unbranched and is even more preferably methylene or ethylene, furthermore preferably propylene or butylene.

- 5 In compounds of formula I, alkylencycloalkyl more preferably has 5 to 10 carbon atoms and is even more preferably methylenecyclopropyl, methylenecyclobutyl, furthermore preferably methylenecyclopentyl, methylenecyclohexyl or methylenecycloheptyl, furthermore alternatively ethylenecyclopropyl, ethylenecyclobutyl, ethylenecyclopentyl, ethylenecyclohexyl or ethylenecycloheptyl, propylenecyclopentyl, propylenecyclohexyl, butylenecyclopentyl or butylenecyclohexyl.
- 10

- In compounds of formula I, the term "alkoxy" more preferably comprises groups of formula O-alkyl, where alkyl is an alkyl group as defined above.
- 15 Even more preferred, alkoxy is selected from group consisting of methoxy, ethoxy, n-propoxy, isopropoxy, 2-butoxy, tert.-butoxy and halogenated, especially perhalogenated, derivatives thereof. Preferred perhalogenated derivatives are selected from the group consisting of O-CCl₃, O-CF₃, O-C₂Cl₅, O-C₂F₅, O-C(CCl₃)₃ and O-C(CF₃)₃.

20

- In compounds of formula I, the term "alkoxyalkyl" more preferably comprises branched and unbranched residues, even more preferred unbranched residues, of formula C_uH_{2u+1}-O-(CH₂)_v, wherein u and v are independently from each other 1 to 6. Especially preferred is u = 1 and v = 1 to 4.
- 25

- In compounds of formula I the term "alkoxyalkyl" includes alkoxyalkyl groups as defined above, wherein one or more of the hydrogen atoms are substituted by halogen, for example up to perhalo alkoxyalkyl.

30

In compounds of formula I, cycloalkyl more preferably has 3 – 7 carbon atoms and is even more preferred cyclopropyl or cyclobutyl, furthermore

preferably cyclopentyl or cyclohexyl, furthermore also cycloheptyl, particularly preferably cyclopentyl.

5 In compounds of formula I, Ar³ to Ar⁶ are more preferably selected independently from one another from phenyl, naphthyl and biphenyl which is optionally substituted by one or more substituents, selected from the group consisting of A, Hal, NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶, NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵, SO₂R¹⁵R¹⁶, S(O)_uA and OOCR¹⁵.

10 In compounds of formula I, het is more preferably an optionally substituted aromatic heterocyclic residue and even more preferred an optionally substituted saturated heterocyclic residue, wherein the substituents are preferably selected from A, CN and Hal. Even more preferred, het is
15 selected from the group consisting of 1-piperidyl, 1-piperazyl, 1-(4-methyl)-piperazyl, 4-methylpiperazin-1-yl amine, 4-morpholinyl, 1-4pyrrolidinyl, 1-pyrazolidinyl 1-(2-methyl)-pyrazolidinyl, 1-imidazolidinyl or 1-(3-methyl)-imidazolidinyl, thiophen-2-yl, thiophen-3-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl,
20 chinolinyl, isochinolinyl, 2-pyridazyl, 4-pyridazyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 2-pyrazinyl and 3-pyrazinyl.

A preferred aspect of the instant invention relates to compounds of formula I, wherein n is 0 or 1 and especially 0.

25

Another preferred aspect of the instant invention relates to compounds of formula I, wherein n is 0 in the residues R⁸, R⁹ and/or R¹⁰ and especially in R¹⁰.

30

Another preferred aspect of the instant invention relates to compounds of formula I, wherein X represents a bridging group, selected from (CR¹¹R¹²)_n or (CHR¹¹)_n-Q-(CHR¹²)_i.

If the bridging group X is $(CR^{11}R^{12})_h$, h is preferably selected from 0, 1, 2, 3 and 4, more preferably from 1, 2, 3 and 4 and especially from 1 or 2.

- 5 If the bridging group X is $(CHR^{11})_h-Q-(CHR^{12})_i$, h and/or i are preferably selected from 0, 1, 2, 3 and 4, more preferably from 0, 1, 2 and 3 and especially from 0, 1 or 2, and even more preferred, both h and i are 0.

10 The invention relates in particular to compounds of the formula I in which at least one of said radicals has one of the preferred meanings given above.

15 Some more preferred groups of compounds may be expressed by the following sub-formulae I.1) to I.18), which correspond to the formula I and in which radicals not denoted in greater detail are as defined in the formula I, but in which

I.1) p is 1, 2 or 3;

20 I.2) p is 1, 2 or 3,

25 R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$;

30 I.3) p is 1, 2 or 3,

- 5 R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$,
- 10 n is 0, 1 or 2, preferably 0 or 1;
- 1.4) p is 1, 2 or 3,
- 15 R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$,
- 20 n is 0, 1 or 2, preferably 0 or 1, and
 q is 0 or 1;
- 25 1.5) p is 1, 2 or 3,
- 30 R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$,

- 5 n is 0, 1 or 2, preferably 0 or 1,
- q is 0 or 1, and
- X is selected from the group consisting of O, S, NR¹¹,
CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂,
CH₂CH₂O, preferably O, S and CH₂ and especially O
and S;
- 10 I.6) p is 1, 2 or 3,
- R⁸ is selected from the group consisting of alkyl comprising
1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon
15 atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising
1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹²,
(CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³,
(CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and
20 (CH₂)_nS(O)_uR¹³,
- n is 0, 1 or 2, preferably 0 or 1,
- q is 0 or 1, and
- 25 X is selected from the group consisting of O, S, NR¹¹,
CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂,
CH₂CH₂O, preferably O, S and CH₂ and especially O
and S,
- 30 Ar² is phenyl, pyridinyl or pyrimidyl, and especially is phenyl
or pyridinyl;

- 1.7) p is 1, 2 or 3,
- R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$,
- n is 0, 1 or 2, preferably 0 or 1,
- q is 0 or 1, and
- X is selected from the group consisting of O, S, NR^{11} , $CHOR^{11}$, CH_2 , CH_2CH_2 , OCH_2 , CH_2O , OCH_2CH_2 , CH_2CH_2O , preferably O, S and CH_2 and especially O and S,
- Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
- R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$;

- 1.8) p is 1, 2 or 3,
- 5 R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$,
- 10
- n is 0, 1 or 2, preferably 0 or 1,
- 15 q is 0 or 1, and
- X is selected from the group consisting of O, S, NR^{11} , $CHOR^{11}$, CH_2 , CH_2CH_2 , OCH_2 , CH_2O , OCH_2CH_2 , CH_2CH_2O , preferably O, S and CH_2 and especially O and S,
- 20
- Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
- 25 R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$,
- 30

$(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,

k is 0, 1 or 2, preferably 0 or 2;

5

1.9) p is 1, 2 or 3,

R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$,

10

15

n is 0, 1 or 2, preferably 0 or 1,

q is 0 or 1, and

20 X is selected from the group consisting of O, S, NR¹¹,
CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂,
CH₂CH₂O, preferably O, S and CH₂ and especially O
and S.

25 Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and

R¹⁰ is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOR¹³,

30

- $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$
 and $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$, preferably selected from the group
 consisting of alkyl comprising 1 to 4 carbon atoms,
 $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,
- k is 0, 1 or 2, preferably 0 or 2 and
- r is 0, 1 or 2, preferably 0 or 1;
- I.10) R^8 is selected from the group consisting of alkyl comprising
 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon
 atoms, Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, perhaloalkyl comprising
 1 to 4 carbon atoms, NO_2 , $(\text{CH}_2)_n\text{CN}$, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$,
 $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$,
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and
 $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$,
- n is 0, 1 or 2, preferably 0 or 1,
- q is 0 or 1, and
- X is selected from the group consisting of O, S, NR^{11} ,
 CHOR^{11} , CH_2 , CH_2CH_2 , OCH_2 , CH_2O , OCH_2CH_2 ,
 $\text{CH}_2\text{CH}_2\text{O}$, preferably O, S and CH_2 and especially O
 and S,
- Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl
 or pyridinyl, and

- 37 -

- 5 R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$,
- 10
- k is 0, 1 or 2, preferably 0 or 2 and
- 15 r is 0, 1 or 2, preferably 0 or 1;
- 20 I.11) R^8 is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$,
- 25 q is 0 or 1, and
- 30 X is selected from the group consisting of O, S, NR^{11} , $CHOR^{11}$, CH_2 , CH_2CH_2 , OCH_2 , CH_2O , OCH_2CH_2 , CH_2CH_2O , preferably O, S and CH_2 and especially O and S,

- 38 -

- Ar² is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
- 5 R¹⁰ is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹² and especially (CH₂)_nCONR¹¹R¹²,
- 10
- 15 k is 0, 1 or 2, preferably 0 or 2 and
- r is 0, 1 or 2, preferably 0 or 1;
- 20 I.12) R⁸ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³,
- 25
- 30 X is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂, CH₂CH₂O, preferably O, S and CH₂ and especially O and S,

- Ar² is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
- 5 R¹⁰ is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³, preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹² and especially (CH₂)_nCONR¹¹R¹²,
- 10
- 15 k is 0, 1 or 2, preferably 0 or 2 and
- r is 0, 1 or 2, preferably 0 or 1;
- 20 I.13) R⁸ is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH₂Hal, CH(Hal)₂, perhaloalkyl comprising 1 to 4 carbon atoms, NO₂, (CH₂)_nCN, (CH₂)_nNR¹¹R¹², (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOR¹³, (CH₂)_nCOOR¹³, (CH₂)_nCONR¹¹R¹², (CH₂)_nSO₂NR¹¹R¹² and (CH₂)_nS(O)_uR¹³,
- 25
- q is 0 or 1, and
- 30 X is selected from the group consisting of O, S, NR¹¹, CHOR¹¹, CH₂, CH₂CH₂, OCH₂, CH₂O, OCH₂CH₂,

$\text{CH}_2\text{CH}_2\text{O}$, preferably O, S and CH_2 and especially O and S,

- 5 R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(\text{CH}_2)_n\text{CN}$, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$ and $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$, preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,
- 10
- 15 k is 0, 1 or 2, preferably 0 or 2 and
- r is 0, 1 or 2, preferably 0 or 1;
- 20 I.14) q is 0 or 1, and
- X is selected from the group consisting of O, S, NR^{11} , CHOR^{11} , CH_2 , CH_2CH_2 , OCH_2 , CH_2O , OCH_2CH_2 , $\text{CH}_2\text{CH}_2\text{O}$, preferably O, S and CH_2 and especially O and S,
- 25
- Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
- 30 R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, perhaloalkyl

- comprising 1 to 4 carbon atoms, NO_2 , $(\text{CH}_2)_n\text{CN}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$
 5 and $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$, preferably selected from the group
 consisting of alkyl comprising 1 to 4 carbon atoms,
 $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,
- 10 k is 0, 1 or 2, preferably 0 or 2 and
- r is 0, 1 or 2, preferably 0 or 1;
- I.15) X is selected from the group consisting of O, S, NR^{11} ,
 15 CHOR^{11} , CH_2 , CH_2CH_2 , OCH_2 , CH_2O , OCH_2CH_2 ,
 $\text{CH}_2\text{CH}_2\text{O}$, preferably O, S and CH_2 and especially O
 and S,
- Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl
 20 or pyridinyl, and
- R^{10} is selected from the group consisting of H, alkyl
 comprising 1 to 4 carbon atoms, alkoxy comprising 1 to
 4 carbon atoms, Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, perhaloalkyl
 25 comprising 1 to 4 carbon atoms, NO_2 , $(\text{CH}_2)_n\text{CN}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$
 and $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$, preferably selected from the group
 consisting of alkyl comprising 1 to 4 carbon atoms,
 30 $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,

- k is 0, 1 or 2, preferably 0 or 2 and
 r is 0, 1 or 2, preferably 0 or 1;
- 5 I.16) Ar^2 is phenyl, pyridinyl or pyrimidyl, and especially is phenyl or pyridinyl, and
 R^{10} is selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$ and especially $(CH_2)_nCONR^{11}R^{12}$,
- 10
 15
 20 k is 0, 1 or 2, preferably 0 or 2 and
 r is 0, 1 or 2, preferably 0 or 1;
- 25 I.17) R^{10} is selected from the group consisting of H, alkyl comprising 1 to 4 carbon atoms, alkoxy comprising 1 to 4 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, perhaloalkyl comprising 1 to 4 carbon atoms, NO_2 , $(CH_2)_nCN$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nSO_2NR^{11}R^{12}$ and $(CH_2)_nS(O)_uR^{13}$, preferably selected from the group consisting of alkyl comprising 1 to 4 carbon atoms, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOR^{13}$,
- 30

- 43 -

$(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$,

k is 0, 1 or 2, preferably 0 or 2 and

5

r is 0, 1 or 2, preferably 0 or 1;

I.18) R^{10} is selected from the group consisting of H, alkyl
 comprising 1 to 4 carbon atoms, alkoxy comprising 1 to
 4 carbon atoms, Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, perhaloalkyl
 comprising 1 to 4 carbon atoms, NO_2 , $(\text{CH}_2)_n\text{CN}$,
 $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$
 and $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$, preferably selected from the group
 consisting of alkyl comprising 1 to 4 carbon atoms,
 $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{COOR}^{13}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially
 $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, and

10

15

20

r is 0, 1 or 2, preferably 0 or 1.

One preferred embodiment of the instant invention relates to compounds
 of formula I and preferably one or more of sub formulae I.1) to I.18),
 wherein p is 1, 2 or 3 and R^8 is independently selected from the group
 consisting of methyl, ethyl, isopropyl, tert.-butyl, F, Cl, Br, CF_3 , $\text{C}(\text{CF}_3)_3$,
 methoxy, ethoxy, tert.-butoxy, perfluoro tert.-butoxy ($\text{OC}(\text{CF}_3)_3$), methyl
 sulfanyl (SCH_3), ethyl sulfanyl (SCH_2CH_3), acetyl (COCH_3), propionyl
 (COCH_2CH_3), butyryl ($\text{COCH}_2\text{CH}_2\text{CH}_3$) and SO_2CF_3 . If p is 2 or 3, all
 substituents can be the same or different.

30

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.19), wherein the sum of h and i exceeds 0.

- 5 Another more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.19), wherein h and/or i are 0.

- 10 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.19), wherein X is selected from the group consisting of O, S, N-R²¹, CH₂, CH₂CH₂, OCH₂, CH₂O, C=O, C(=O)-NH and NH-C(=O).

- 15 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein X is selected from the group consisting of S, N-R²¹, CH₂, CH₂CH₂, OCH₂, CH₂O, C=O, C(=O)-NH and NH-C(=O).

- 20 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein X is selected from the group consisting of S, CH₂.

- 25 Another even more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein X is O.

- 30 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein Y is selected from the group consisting of C(R²²)-NO₂, C(R²²)-CN and C(CN)₂.

Another more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein Y is selected from the group consisting of O, S and NR^{21} .

- 5 Another even more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein Y is selected from the group consisting of O and S.

- 10 Another even more preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein Y is O.

- 15 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein Ar^2 is pyridinyl.

- 20 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein r is either 0 or 1. If r is 1, R^{10} is preferably $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$ and especially $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, wherein n is 0. In this embodiment, R^{11} is preferably selected from the group consisting of H and A, more preferred from H and alkyl and especially is H, and R^{12} is preferably selected from the group consisting of H and A and more preferred from H, unsubstituted alkyl and substituted alkyl, preferably comprising 1 to 6 and especially 1 or
- 25 2 carbon atoms. Suitable for substituents include amino groups, such as NH_2 , NHCH_3 , NHCH_2CH_3 , $\text{N}(\text{CH}_3)_2$ and $\text{NH}(\text{CH}_2\text{CH}_3)$, and carboxyl groups and derivatives thereof, such as COOH , COOCH_3 , CONH_2 , and CONHCH_3 . Especially preferred as residue R^{10} are CONHCH_3 , $\text{CONHCH}_2\text{CH}_2\text{NH}_2$, $\text{CONHCH}_2\text{CH}_2\text{NHCH}_3$, $\text{CONHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$,
- 30 $\text{CONHCH}_2\text{COOH}$ and $\text{CONHCH}_2\text{CH}_2\text{COOH}$. This embodiment is especially preferred when Ar^2 is pyridinyl. When Ar^2 is pyridinyl, R^{10} is

preferably bonded in a vicinal position to the nitrogen atom of the pyridinyl residue, i.e. in 2- and/or 6-position of the pyridinyl residue.

Another preferred embodiment of the instant invention relates to
 5 compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein the benzimidazole-moiety comprises two or more substituents R^8 , wherein one or more, preferably one substituent R^8 is selected from the group consisting of $(CH_2)_nNR^{11}R^{12}$,
 $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{12}R^{12}$,
 10 $(CH_2)_nCOOR^{13}$ and $(CH_2)_nS(O)_uR^{13}$ wherein R^{11} , R^{12} and R^{13} are defined as above and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2, and u is preferably 2. In this embodiment R^{11} , R^{12} and R^{13} are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. In this
 15 embodiment, one or two substituents R^8 and preferably one substituent R^8 is especially preferably selected from the group consisting of NH_2 , $N(CH_3)_2$, $N(C_2H_5)_2$, $NHCH_2CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$, SCH_3 , SC_2H_5 , SO_2CH_3 , $COOCH_3$ and $COOH$.
 20 Accordingly, in this embodiment the benzimidazole-moiety especially preferably comprises at least one substituent R^8 other than $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{12}R^{12}$, $(CH_2)_nCOOR^{13}$ and $(CH_2)_nS(O)_uR^{13}$ as defined in this paragraph and especially other than NH_2 , $N(CH_3)_2$, $N(C_2H_5)_2$, $NHCH_2CH_2NH_2$,
 25 $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$, SCH_3 , SC_2H_5 , SO_2CH_3 , $COOCH_3$ and $COOH$.

Another preferred embodiment of the instant invention relates to
 30 compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein q is 1, i.e. the phenylen moiety bound to the oxamide group and the radical X is substituted once, preferably by a substituent selected

from the group consisting of alkyl and halogen and more preferred from methyl, ethyl, F, Cl and Br .

Another preferred embodiment of the instant invention relates to
 5 compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein q is 0, i.e. the phenylene moiety bound to the oxamide group and the radical X is unsubstituted.

Another preferred embodiment of the instant invention relates to
 10 compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein the $(R^8)_p$ -benzimidazole-moiety is as defined above, but comprises one or more additional residues, preferably one additional residue. The additional residues are preferably selected from the meanings given for R^8 and more preferably selected from the group
 15 consisting of $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nNR^{11}(CH_2)_kOR^{12}$, $(CH_2)_nNR^{11}(CH_2)_kNR^{12}R^{12}$, $(CH_2)_nCOOR^{13}$ and $(CH_2)_nS(O)_uR^{13}$ wherein R^{11} , R^{12} and R^{13} are defined as above and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2, and u is preferably 2. In this embodiment R^{11} , R^{12} and
 20 R^{13} are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. Even more preferred, the additional residue(s) is/are selected from the group consisting of NH_2 , $N(CH_3)_2$, $N(C_2H_5)_2$, $NHCH_2CH_2NH_2$, $N(CH_3)CH_2CH_2NH_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$,
 25 $OCH_2CH_2N(CH_3)_2$, SCH_3 , SC_2H_5 , SO_2CH_3 , $COOCH_3$ and $COOH$.

Another preferred embodiment of the instant invention relates to
 compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein X is bonded in the para- (p-) or metha- (m-)position to the
 30 phenyl residue that is bonded directly to the oxamide moiety.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein Ar^2 is a pyridinyl residue and wherein said pyridinyl residue is bonded to X in the 3- or 4-position, preferably the 4-position, relative to the nitrogen atom of the pyridinyl residue.

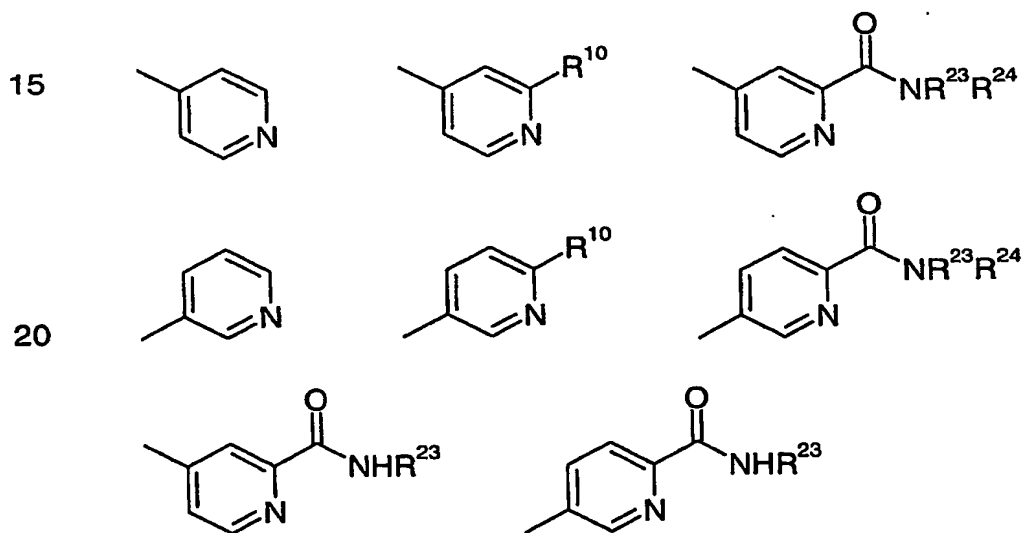
Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein Ar^2 comprises one or more substituents R^{10} and wherein one or two, preferably one substituent R^{10} is selected from unsubstituted or substituted carbamoyl moieties. Substituted carbamoyl moieties are preferably selected from $CONHR^{23}$ or $CONR^{23}R^{24}$, preferably $CONHR^{23}$, wherein R^{23} and R^{24} are independently selected from the definitions given for R^8 , more preferably selected from alkyl, preferably methyl, ethyl, propyl and butyl, $(CH_2)_nNR^{11}R^{12}$ and $(CH_2)_nOR^{12}$, wherein R^{11} , R^{12} and n are as defined above. In this embodiment, n is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for R^{23} are selected from the group consisting of methyl, ethyl, $CH_2CH_2NH_2$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2N(CH_2CH_3)_2$, CH_2CH_2OH , $CH_2CH_2OCH_3$ and $CH_2CH_2OCH_2CH_3$.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein Ar^2 comprises one or more substituents R^{10} and wherein one or two, preferably one substituent R^{10} is selected from substituted carbamoyl moieties. Substituted carbamoyl moieties are preferably selected from $CONHR^{23}$, wherein R^{23} is preferably unsubstituted C_1 - C_4 -alkyl and especially methyl.

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein Ar^2 comprises one or more substituents R^{10} and wherein

one or two, preferably one substituent R^{10} is selected from substituted carbamoyl moieties. Substituted carbamoyl moieties are preferably selected from $CONHR^{23}$, wherein R^{23} is selected from $(CH_2)_nNR^{11}R^{12}$ and $(CH_2)_nOR^{12}$, wherein R^{11} , R^{12} and n are as defined above. In this
 5 embodiment, n is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for R^{23} are selected from the group consisting of $CH_2CH_2NH_2$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2N(CH_2CH_3)_2$, CH_2CH_2OH , $CH_2CH_2OCH_3$ and $CH_2CH_2OCH_2CH_3$.

10 Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein $-Ar^2-(R^{10})$ is selected from the formulae

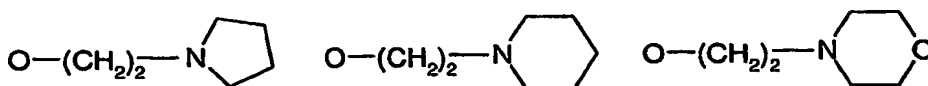


wherein R^{10} , R^{23} and R^{24} are as defined above and below.

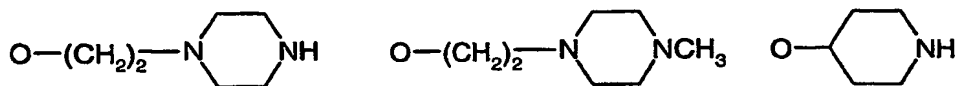
Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein the benzimidazole-moiety comprises one or more
 30 substituents R^8 and wherein one or two, preferably one substituent R^8 is selected from the group consisting of NH_2 , $N(CH_3)_2$, $NHCH_3$, $N(C_2H_5)_2$,

HNCH₂CH₂NH₂, OCH₂CH₂NH₂, HOCH₂CH₂NH, OCH₂CH₂NHCH₃,
 N(CH₃)CH₂CH₂NH₂, HN(CH₃)CH₂CH₂NH, N(CH₃)CH₂CH₂N(CH₃)₂,
 N(CH₃)CH₂CH₂N(CH₃)₂, N(CH₃)CH₂CH₂OCH₃, OCH₂CH₂N(CH₃)₂,
 OCH₂CH₂N(CH₂CH₃)₂, SCH₃, SC₂H₅, and compounds of the formulae

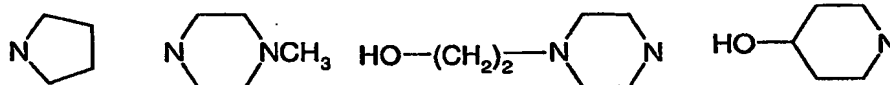
5



10



15



and/or Ar² comprises one or more substituents R¹⁰ and wherein one or two, preferably one substituent R¹⁰ is independently selected from the meanings given for R⁸ in this paragraph.

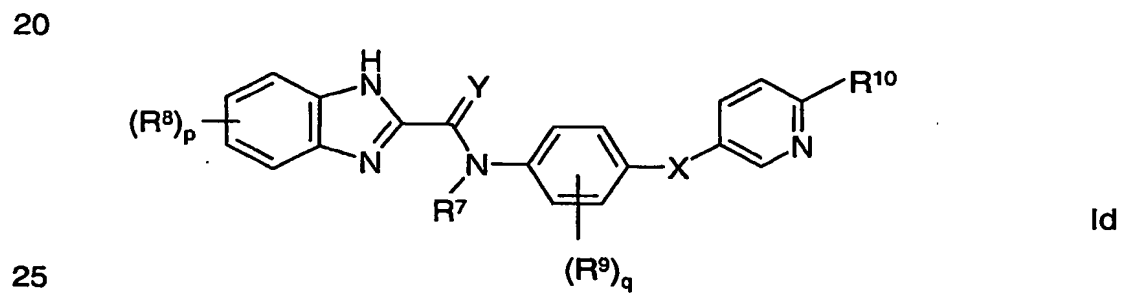
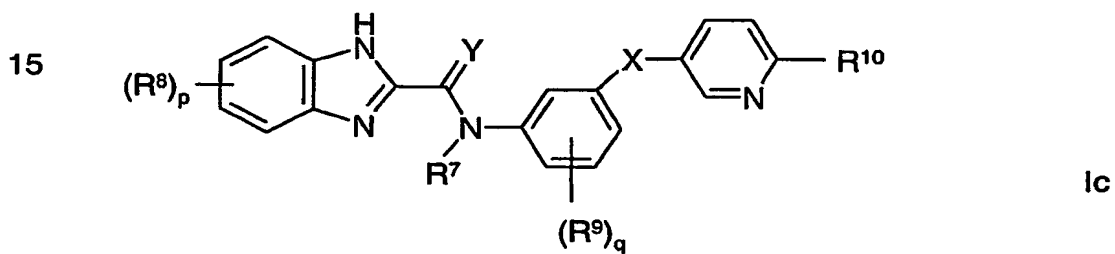
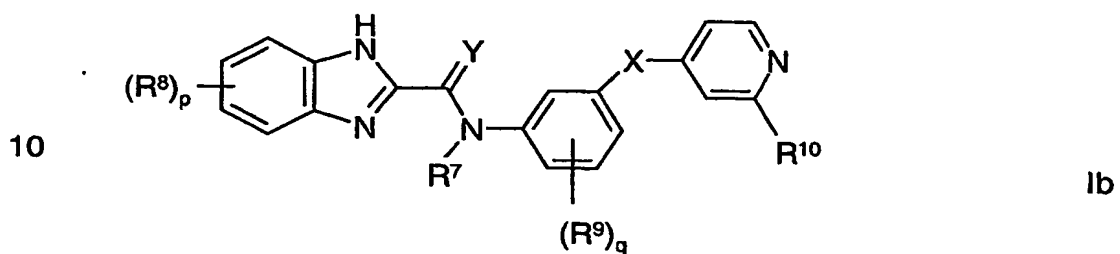
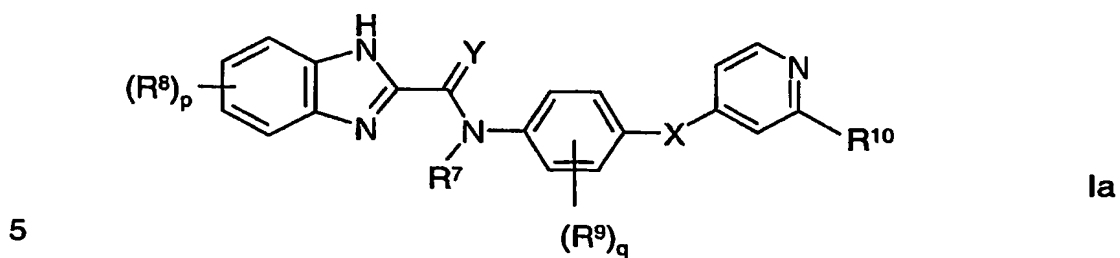
20

Another especially preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18), wherein one or more features of the above and below mentioned embodiments are combined in one compound.

25

Subject of the present invention are therefore especially preferred compounds of formula I according to one or more of the formulae Ia, Ib, Ic and Id,

30



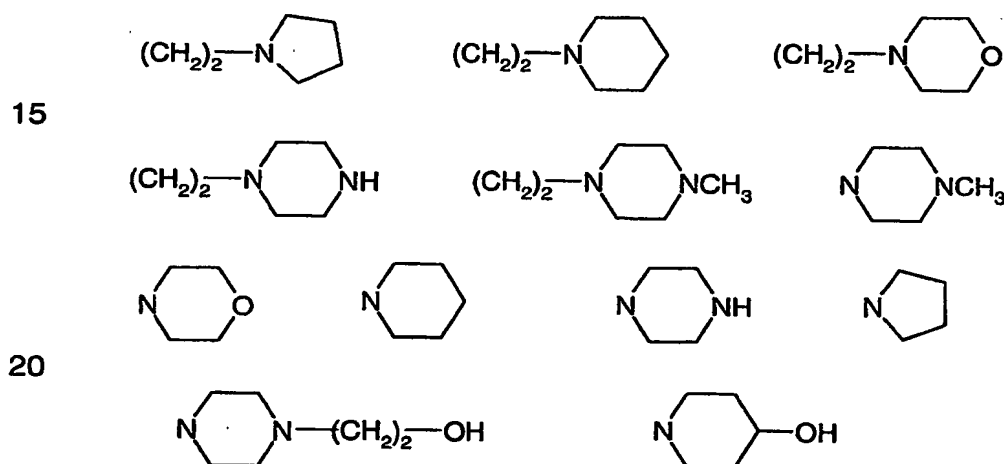
wherein R^8 , p , X , Y , R^9 and q are as defined above and below, and R^{10} is H or as defined above and below, and preferably all are as defined in sub formulae I.1) to I.18) and/or the embodiments related thereto.

30

Another preferred embodiment of the instant invention relates to compounds of formula I and preferably one or more of sub formulae I.1) to I.18) and Ia to Id, wherein R^{10} is a substituted carbamoyl moiety $CONHR^{23}$ or $CONR^{23}R^{24}$, preferably $CONHR^{23}$, wherein R^{23} and R^{24} are

5 independently selected from the definitions given for R^8 , more preferably selected from $(CH_2)_nNR^{11}R^{12}$ and $(CH_2)_nOR^{12}$, wherein R^{11} , R^{12} and n are as defined above. In this embodiment, n is preferably not 0 and more preferred 1 to 3 and especially 1 or 2. Preferred examples for R^{23} are

10 selected from the group consisting of $CH_2CH_2NH_2$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2N(CH_2CH_3)_2$, CH_2CH_2OH , $CH_2CH_2OCH_3$, $CH_2CH_2OCH_2CH_3$ and from the formulae



It is understood that when a residue, for example R^8 , R^9 , R^{10} or R^{14} or R^{23} , is comprised twice or more times in one or more of the formulae I and the sub formulae corresponding thereto, it is in each case independently from one another selected from the meanings given for the respective residue. For example, R^{11} and R^{12} are defined to be independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$. Then

25

30 $(CH_2)_nNR^{11}(CH_2)_mNR^{12}R^{12}$ can be $(CH_2)_nNA(CH_2)_mNA_2$ (if $R^{11} = A$, $R^{12} = A$ and $R^{12} = H$) as well as $(CH_2)_nNA(CH_2)_mNHA$ (if $R^{11} = A$, $R^{12} = H$ and $R^{12} = A$ or $(CH_2)_nNA(CH_2)_mNH(CH_2)_mHet$ (if $R^{11} = A$, $R^{12} = H$ and $R^{12} =$

(CH₂)_mHet). Accordingly, if a compound of formula I comprises one residue R⁸, R⁹ and R¹⁰, then for example R⁸, R⁹ and R¹⁰ can all be (CH₂)_nCOOR¹³, wherein all residues R¹³ are the same (for example CH₂Hal, wherein Hal is Cl; then all residues R⁸, R⁹ and R¹⁰ are the same) or different (for example CH₂Hal, wherein in R⁸ Hal is Cl; in R⁹ Hal is F; and in R¹⁰ Hal is Br; then all residues R⁸, R⁹ and R¹⁰ are different); or for example R⁸ is (CH₂)_nCOOR¹³, R⁹ is NO₂ and R¹⁰ is (CH₂)_nSR¹¹, wherein R¹¹ and R¹³ can be the same (for example both can be H or both can be A which is methyl) or different (for example R¹¹ can be H and R¹³ can be A which is methyl).

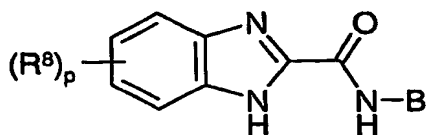
10

If not stated otherwise, reference to compounds of formula I also includes the sub formulae related thereto, especially sub formulae I.1) to I.18) and Ia to Id.

15 Subject of the instant invention are especially those compounds of formula I in which at least one of the residues mentioned in said formulae has one of the preferred or especially preferred meanings given above and below.

The present invention further relates to compounds of formula Ie

20



(Ie) ,

25

wherein

(R⁸)_p denotes no substituent;

(R⁸)_p is 5-Cl;

(R⁸)_p is 5-CF₃;

(R⁸)_p is 4-CH₃ and 5-Cl;

30

(R⁸)_p is 4-Br and 6-CF₃;

(R⁸)_p is 5-Cl and 6-CF₃;

(R⁸)_p is 4-CH₃;

(R⁸)_p is 4-Cl, 6-CF₃;

(R⁸)_p is 5-Cl and 6-CH₃;

(R⁸)_p is 4-CF₃ and 6-CF₃;

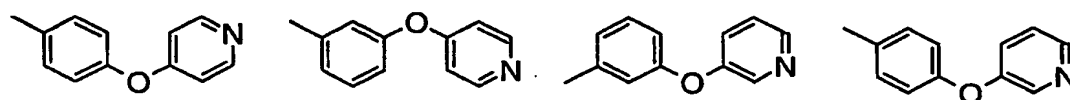
5 (R⁸)_p is 5-Cl and 6-Cl;

and/or

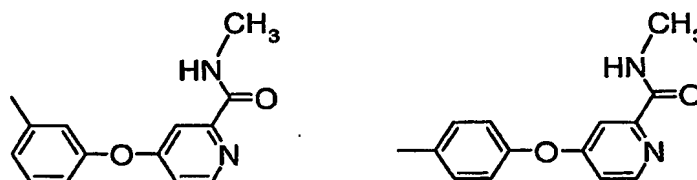
(R⁸)_p is 5-CH₃;

and wherein B is selected from the group as given below:

10



15

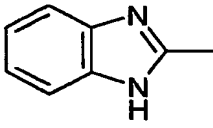
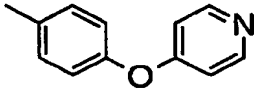
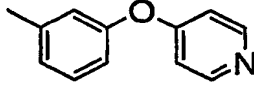
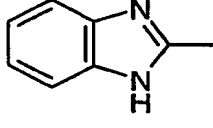
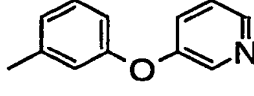
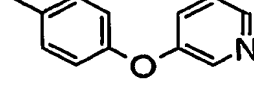
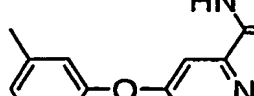



20

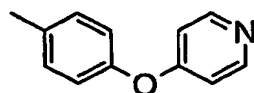
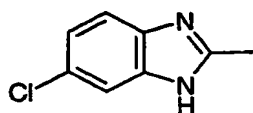
25

30

The present invention further relates to compounds (1) to (72) of formula
A-CO-NH-B, wherein A- and -B are as given in the table below:

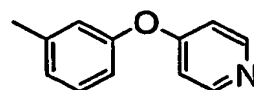
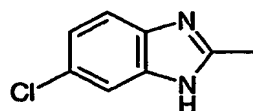
	A-	-B
5		
(1)		
10	(2)	
(3)		
15	(4)	
20	(5)	
25	(6)	
30		

(7)



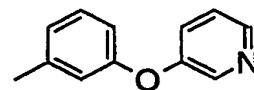
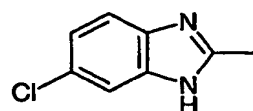
5

(8)

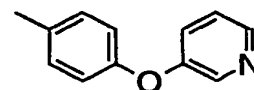
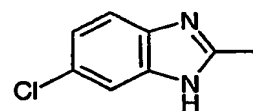


10

(9)

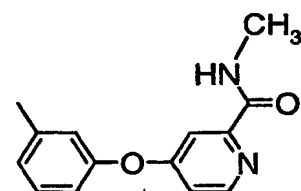
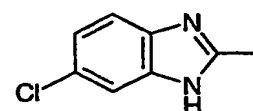


(10)



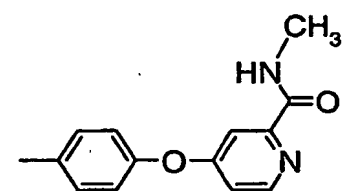
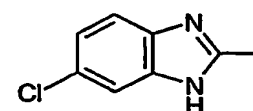
15

(11)



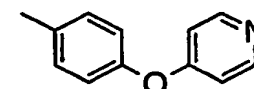
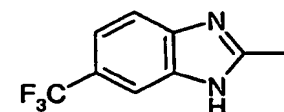
20

(12)



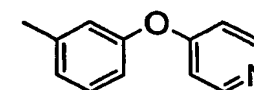
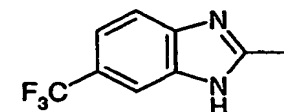
25

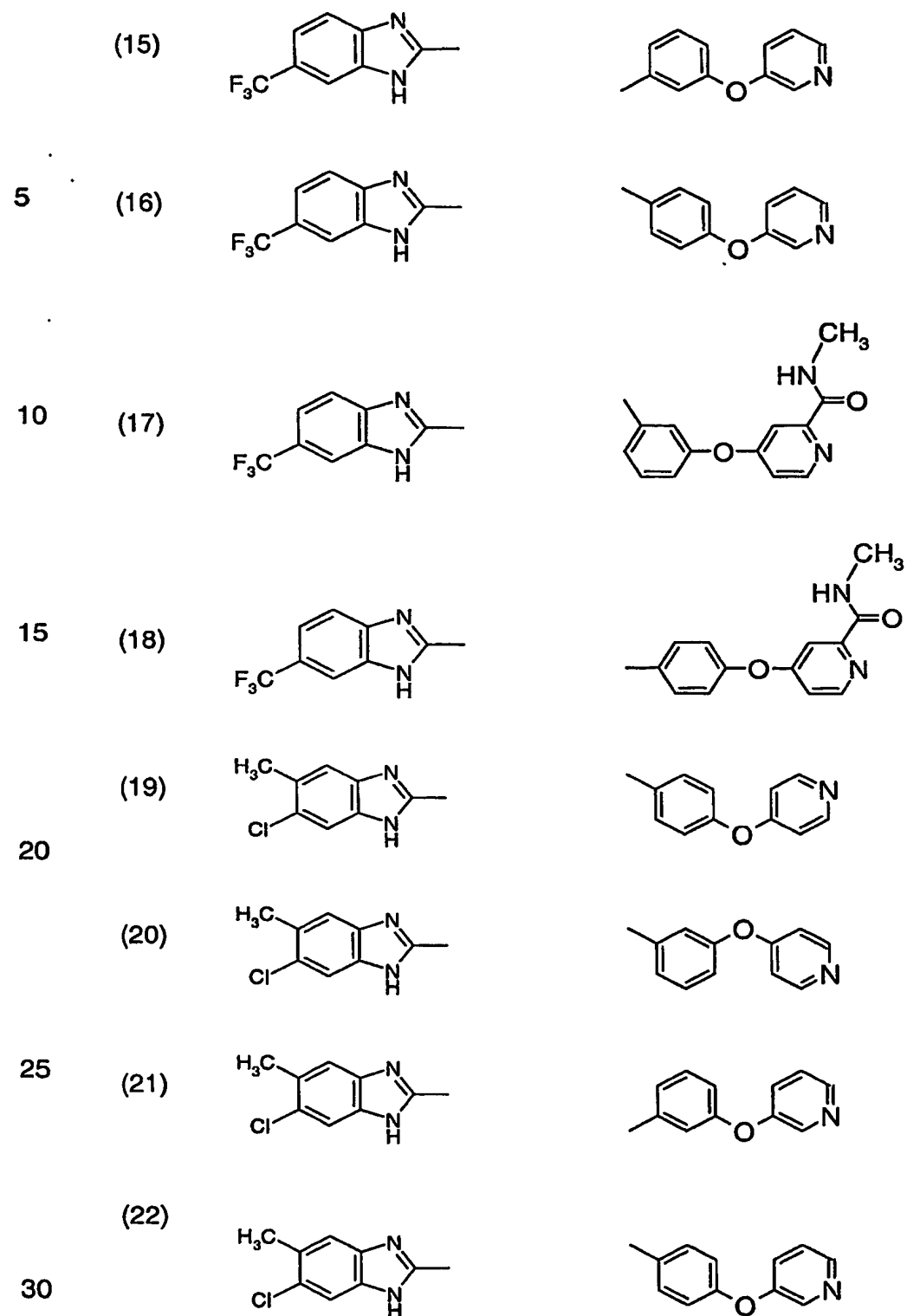
(13)



30

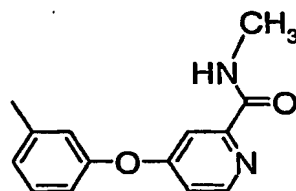
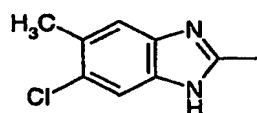
(14)





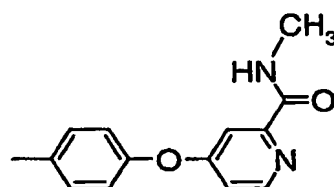
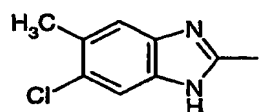
5

(23)



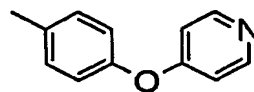
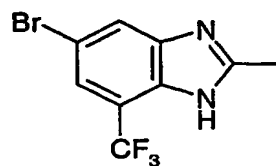
10

(24)

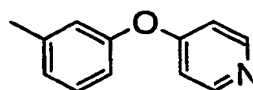
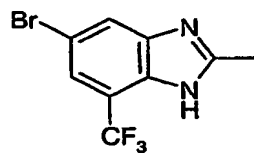


15

(25)

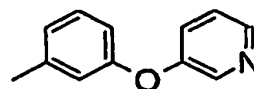
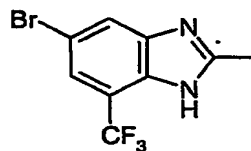


(26)



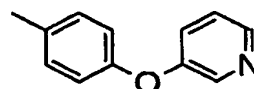
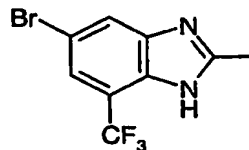
20

(27)



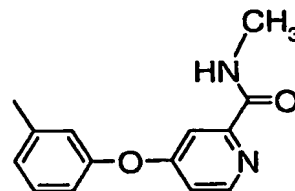
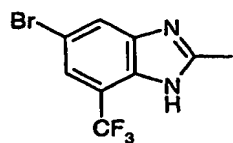
25

(28)



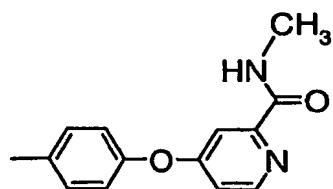
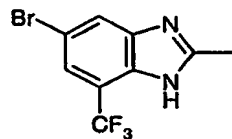
30

(29)

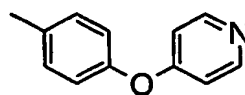
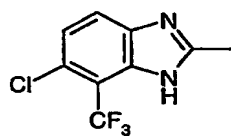


5

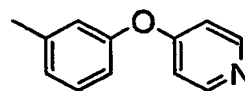
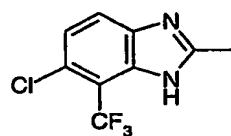
(30)



(31)

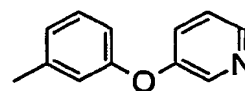
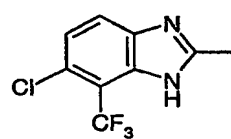


(32)



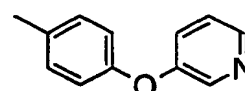
15

(33)



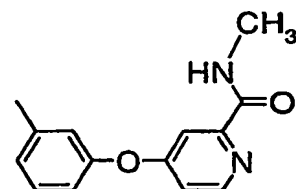
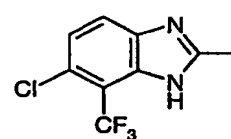
20

(34)



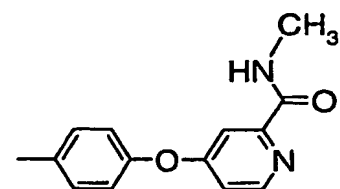
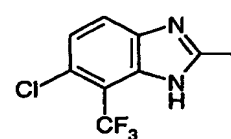
25

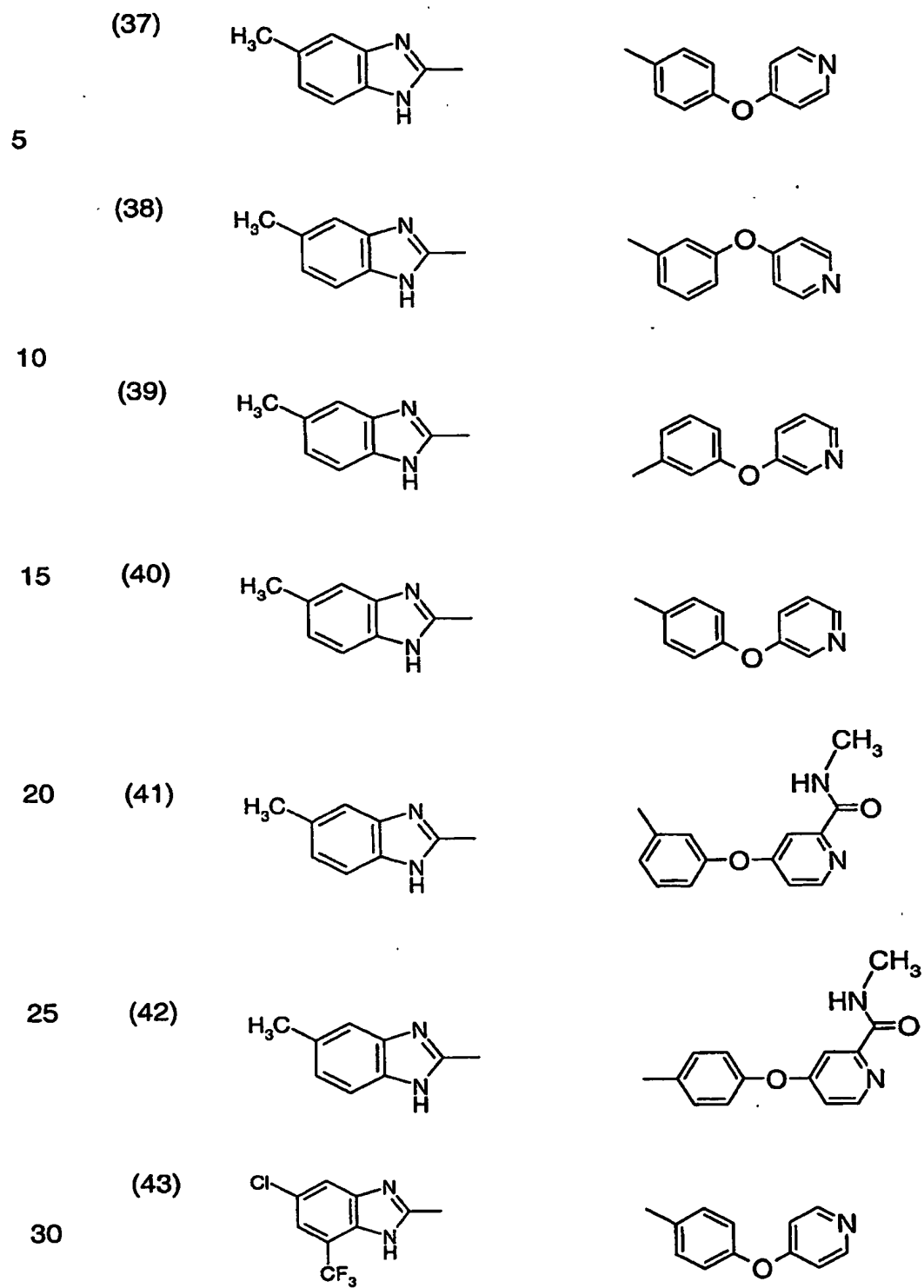
(35)

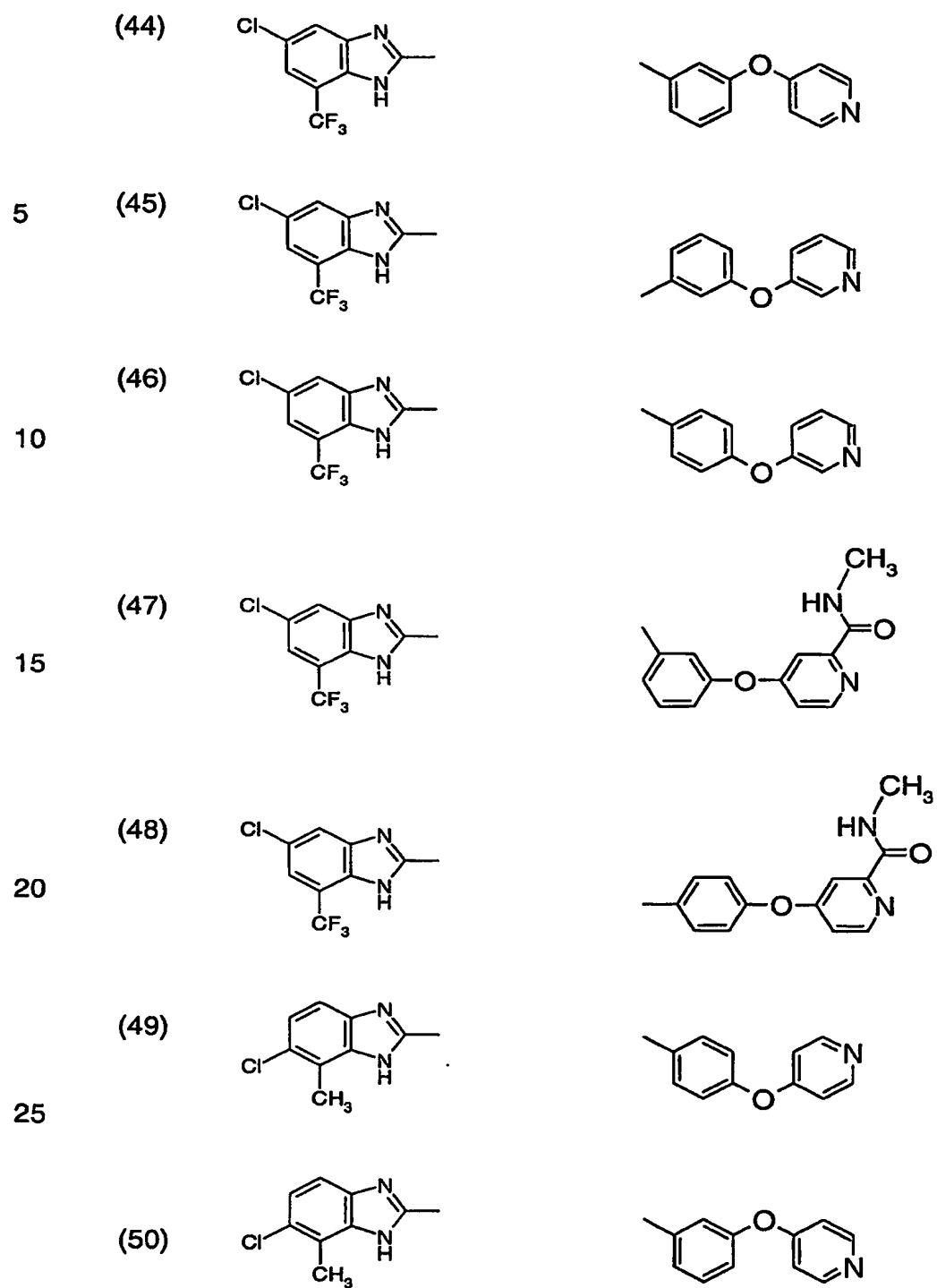


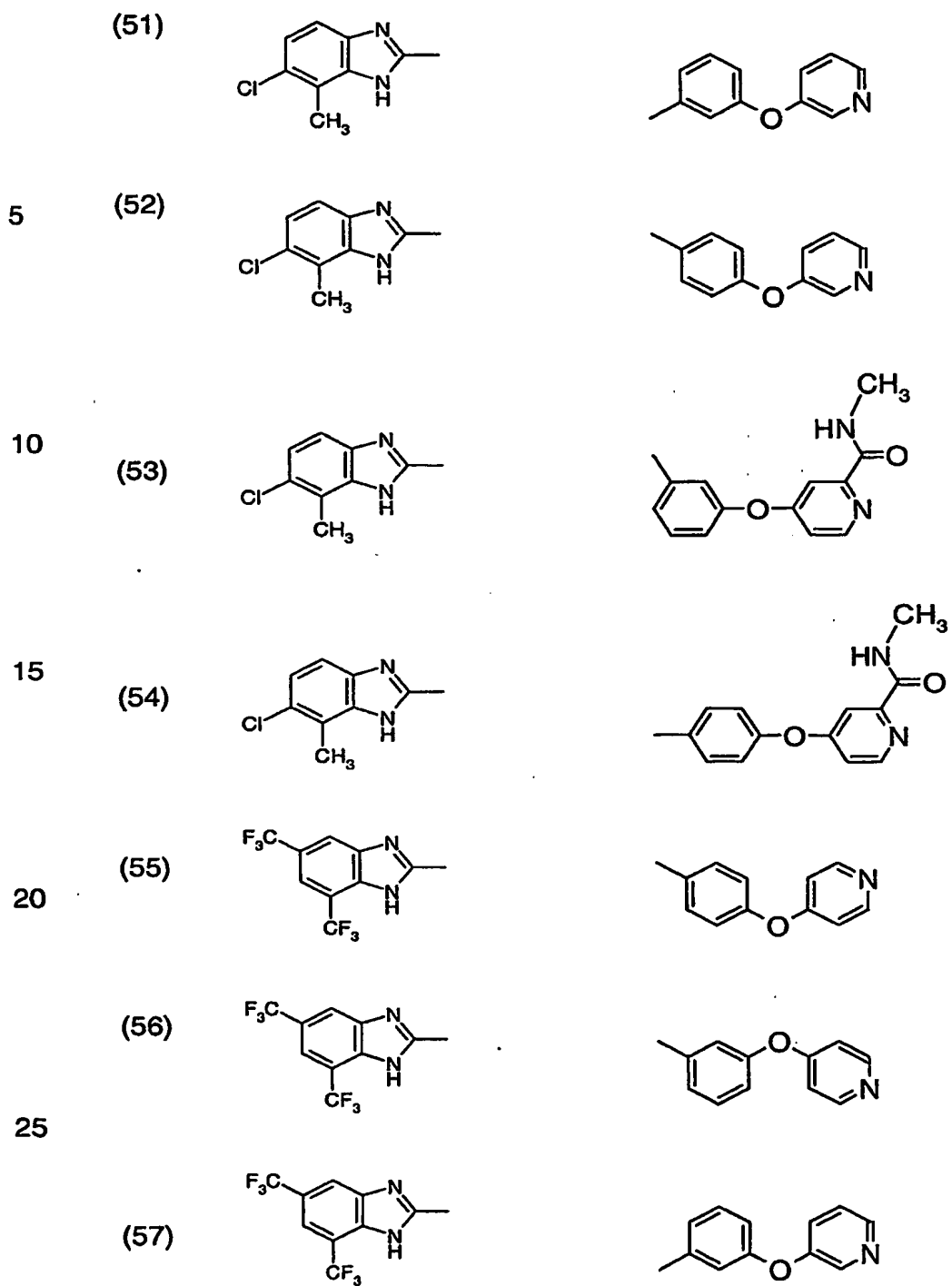
30

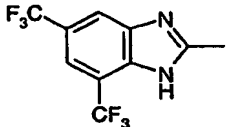
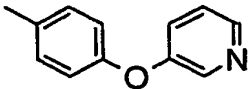
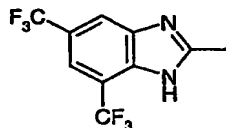
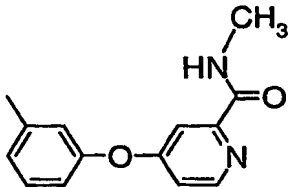
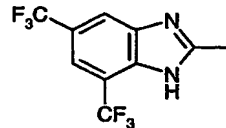
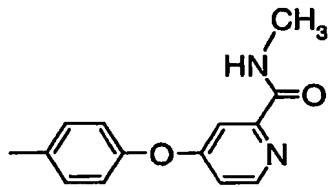
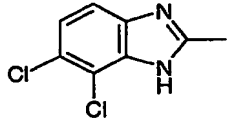
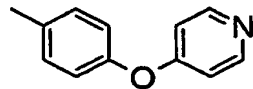
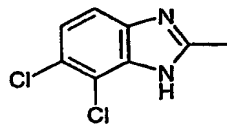
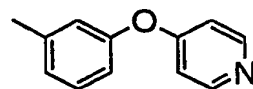

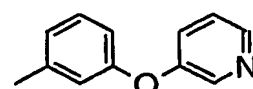
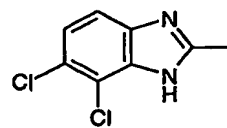
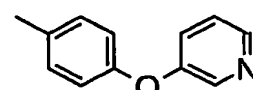
(36)





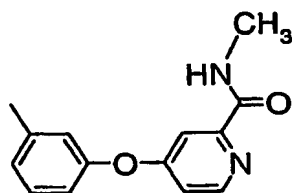
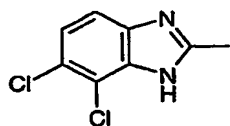




	(58)		
5	(59)		
10	(60)		
15	(61)		
20	(62)		
25	(63)		
30	(64)		

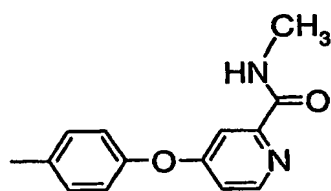
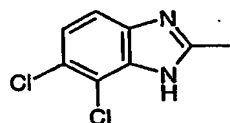
5

(65)



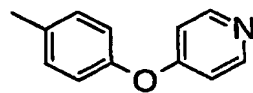
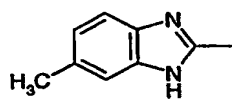
10

(66)



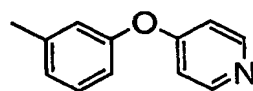
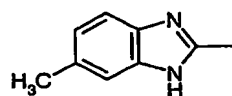
15

(67)



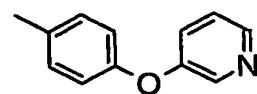
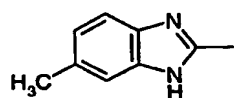
20

(68)



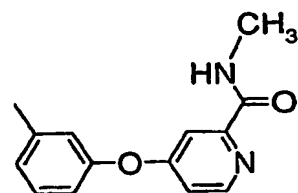
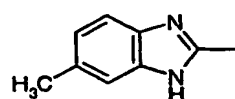
25

(70)



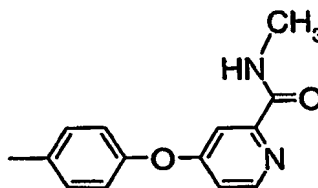
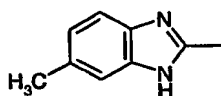
30

(71)



(72)

5



10

In a special embodiment, the benzimidazole carboxamides according to sub formulae Ia, Ib, Ic, Id and/or Ie additionally comprise one or two substituents selected from the group consisting of $O(CH_2)_nNR^{11}R^{12}$, $NR^{11}(CH_2)_nNR^{11}R^{12}$, $O(CH_2)_nOR^{12}$ and $NR^{11}(CH_2)_nOR^{12}$, wherein

R^{11} , R^{12} are independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$, or in $NR^{11}R^{12}$,

15

R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7-membered heterocyclous which optionally contains 1 or 2 additional hetero atoms, selected from N, O and S, and

n is 1, 2, 3, 4, 5 or 6.

20

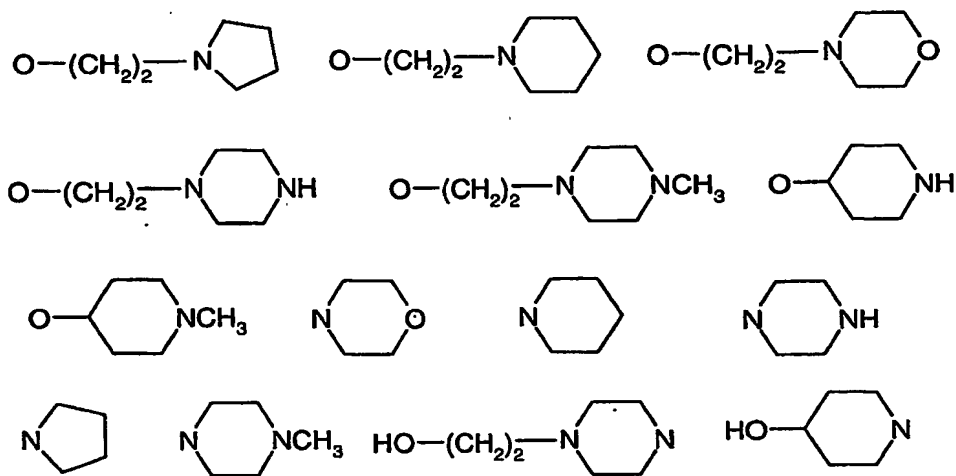
In this embodiment, the substituents are preferably selected from the group consisting of $HNCH_2CH_2NH_2$, $OCH_2CH_2NH_2$, $HOCH_2CH_2NH$, $OCH_2CH_2NHCH_3$, $N(CH_3)CH_2CH_2NH_2$, $HN(CH_3)CH_2CH_2NH$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2N(CH_3)_2$, $N(CH_3)CH_2CH_2OCH_3$, $OCH_2CH_2N(CH_3)_2$, $OCH_2CH_2N(CH_2CH_3)_2$ and compounds of the formulae

25

30

- 66 -

5



10

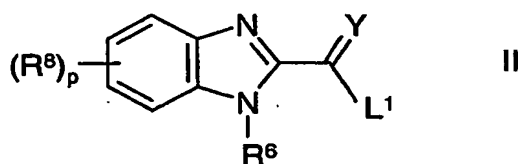
15

The nomenclature as used herein for defining compounds, especially the compounds according to the invention, is in general based on the rules of the IUPAC-organisation for chemical compounds and especially organic compounds.

Another aspect of the invention relates to a method for producing compounds of formula I, characterised in that

20

a) A compound of formula II



25

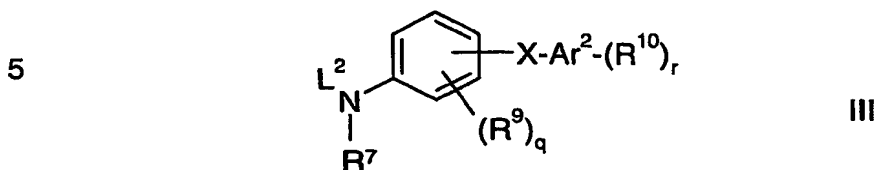
wherein

30

L^1 is Cl, Br, I, OH, an esterified OH-group or a diazonium moiety, and R^6 , R^8 , p and Y are as defined above and below,

is reacted

b) with a compound of formula III,



wherein

10 L^2 is H or a metal ion, and R^7 , R^9 , q , X , Ar^2 , R^{10} and r are as defined above and below,

and optionally

15 c) isolating and/or treating the compound of formula I obtained by said reaction with an acid, to obtain the salt thereof.

20 The compounds of the formula I and also the starting materials for their preparation are, in addition, prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), to be precise under reaction conditions which are known and suitable for the said reactions. Use can
25 also be made here of variants which are known per se, but are not mentioned here in greater detail.

30 If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but instead immediately converting them further into the compounds of the formula I. On the other hand, it is possible to carry out the reaction stepwise.

The compounds of the formula I and especially the compounds of formula I can preferably be obtained by reacting compounds of the formula II with compounds of the formula III.

5 In detail, the reaction of the compounds of the formula II with the compounds of the formula III is carried out in the presence or absence of a preferably inert solvent at temperatures between about -20° and about 200°C , preferably between 0° and 100°C and especially at about room temperature (25°C). In some cases, it can be advantageous to combine
10 one compound of formula II with one compound of formula III at the lower end of the given temperature range, preferably between -20° and 75°C , more preferred between 0° and 60°C and especially between 10° and 40°C , for example at about room temperature, and heat the mixture up to a temperature at the upper end of the given temperature range, preferably
15 between 80° and 180° , more preferred between 90° and 150° and especially between 95° and 120° , for example at about 100° or at about 110° .

20 In general, the compounds of formula II and/or formula III are new. In any case, they can be prepared according to methods known in the art.

In the compounds of formula II, L^1 is preferably Cl, Br, I, OH, a reactive derivatized OH-moiety, especially an esterified OH-moiety, for example an OR'-moiety wherein R' is an alkyl moiety, preferably an alkyl moiety as
25 described above/below comprising 1 to 10 and more preferably 1 to 6 carbon atoms, or a reactive esterified OH-moiety, for example an alkylsulfonyloxy-moiety comprising 1 to 6 carbon atoms (preferably methylsulfonyloxy) or an arylsulfonyloxy-moiety comprising 6 to 10 carbon atoms (preferably phenyl- oder p-tolylsulfonyloxy), or diazonium moiety,
30 more preferred Cl, Br or I and OR', wherein R' is as defined above/below, and even more preferred OH and OR', wherein R' is preferably selected

from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl. Especially preferred as L^1 is OH.

5 In the compounds of formula III, L^2 is preferably H or a moiety which activates the amino group it is bonded to, for example a metal ion. Suitable metal ions are preferably selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions. Especially preferred metal ions are alkaline metal ions, of which Li, Na and K are especially preferred. In case of multi-valent metal ions, the metal ions and
10 the compounds of formula III form a complex containing one or more compounds of formula III and one or more metal ions wherein the ratio between compounds of formula III and metal ions is depending on the valency of the metal ion(s) according to the rules of stoichiometry and/or electroneutrality.

15 The reaction between the compounds of formula II and compounds of formula III can in many cases advantageously be carried out in the presence of an acid binding means, for example one or more bases. Suitable acid binding means are known in the art. Preferred as acid
20 binding means are inorganic bases and especially organic bases. Examples for inorganic bases are alkaline or alkaline-earth hydroxides, alkaline or alkaline-earth carbonates and alkaline or alkaline-earth bicarbonates or other salts of a weak acid and alkaline or alkaline-earth metals, preferably of potassium, sodium, calcium or cesium. Examples for
25 organic bases are triethyl amine, diisopropyl ethyl amine (DIPEA), dimethyl aniline, pyridine or chinoline. If an organic base is used, it is advantageous in general to use a base with a boiling point that is higher than the highest reaction temperature employed during the reaction. Especially preferred as organic base is DIPEA.

30 In many cases, it is advantageous to carry out the reaction of a compound of formula II with a compound of formula III in the presence of one or more

compounds that promote the reaction between the said compounds, for example one or more catalysts and/or one or more compounds that are acting as condensing agents. Suitable compounds in this respect are O-(Benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphat
5 tetrafluoroborate (TBTU), O-(Benzotriazole-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate and 1-Hydroxy-1H-benzotriazole (HOBT).

Reaction times are generally in the range between some minutes and
10 several days, depending on the reactivity of the respective compounds and the respective reaction conditions. Suitable reaction times are readily determinable by methods known in the art, for example reaction monitoring. Based on the reaction temperatures given above, suitable reaction times generally lie in the range between 10 min and 48 hrs,
15 preferably 30 min and 36 hrs and especially between 45 min and 24 hrs, for example about 4 h, about 10 hrs, about 15 hrs or about 20 hrs.

Preferably, the reaction of the compounds of the formula II with the compounds of the formula III is carried out in the presence of a suitable
20 solvent, that is preferably inert under the respective reaction conditions. Examples of suitable solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichlorethylene, 1,2-dichloroethane, tetrachloromethane, chloroform or dichloromethane; alcohols, such as methanol, ethanol,
25 isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP); nitriles, such as acetonitrile; sulfoxides, such
30 as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the said

solvents. Polar solvents are in general preferred. Examples for suitable polar solvents are chlorinated hydrocarbons, alcohols, glycol ethers, nitriles, amides and sulfoxides or mixtures thereof. More preferred are amides, especially dimethylformamide (DMF).

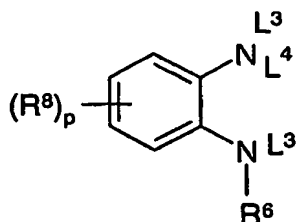
5

If compounds of formula I are desired wherein Y is other than O, it can be advantageous, however, to carry out the reaction of a compound of formula II, wherein Y is O, and a compound of formula III according to the invention to obtain a compound of formula I, wherein Y is O, and to modify or convert the corresponding C=O group (i. e. the C=Y group, wherein Y is O) in the compound of formula I into a C=NR²¹, C=C(R²²)-NO₂, C=C(R²²)-CN or C=C(CN)₂ group according to methods known in the art, for example from Houben-Weyl, Methods of Organic Chemistry.

Especially preferred, the reaction between a compound of formula II, wherein Y is O and L¹ is OH, and a compound of formula III, wherein preferably L² is H, is carried out in the presence of an organic base, such as DIPEA, a polar organic solvent, such as DMF, in the presence of TBTU and HOBT at a temperature between 0 °C and 60 °C, for example at about room temperature. In many cases, it can be advantageous to add an acid at a later stage of the reaction, for example after 2-5 h reaction time, to complete the reaction and/or to facilitate the working up procedure.

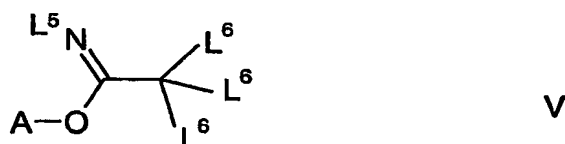
The compounds of formula II can be obtained according to methods known in the art. In an advantageous manner, they can be readily obtained by reacting a compound of formula IV

30



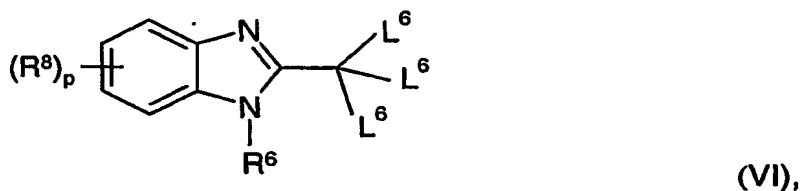
IV

wherein R^6 , R^8 and p are as defined above/below and L^3 and L^4 are selected independently from each other from the meanings given for L^2 and more preferred are hydrogen, with a compound of formula V



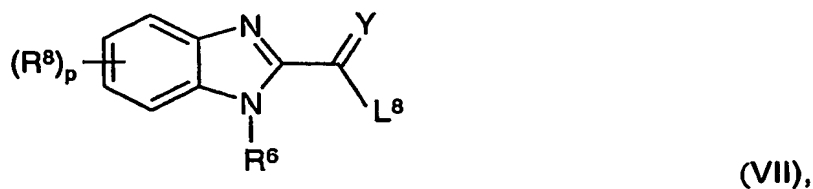
wherein A has the meaning given above/below, L^5 is selected independently from the meanings given for L^2 , and each L^6 is selected independently from one other from the meanings given for L^1 ,

and transforming the obtained compound of formula VI,



wherein R^6 , R^8 and p are as defined above/below and each L^6 is as defined in formula V,

into a compound of formula VII,



wherein R^6 , R^8 , p and Y are as defined above/below and L^8 is selected independently from the meanings given for L^1 ,

for example under solvolysing or preferably hydrolysing conditions.

In compounds of formula V, L^5 is preferably H.

5

In compounds of formula V, A is preferably alkyl, especially preferred alkyl selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl, and especially is methyl.

10

In compounds of formula V and/or VI, L^6 is preferably an OH-moiety and more preferred a derivatized OH-moiety. Preferably, derivatized OH-moieties are OR' -moieties, wherein R' is selected from the meanings given above/below. More preferred, each L^6 is independently selected from the group consisting of Cl, Br and I. In compounds of formula V and/or VI each

15

L^6 is especially preferred Cl.

In Compounds of formula VII, L^8 is preferably OH.

20

Some of the starting materials of the formula IV and/or the formula V are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

25

Suitable reaction conditions for carrying out the reaction of a compound of formula IV with a compound of formula V are known in the art. In detail, the reaction of the compounds of the formula IV with the compounds of the formula V is carried out in the presence or absence of a preferably inert solvent and in the presence or absence of a suitable base at temperatures between about -40° and about 180° , preferably between -20°C and 100° and especially between -10° and 50° , for example at about 0° and/or about room temperature (25°). Especially preferred, the reaction between a

30

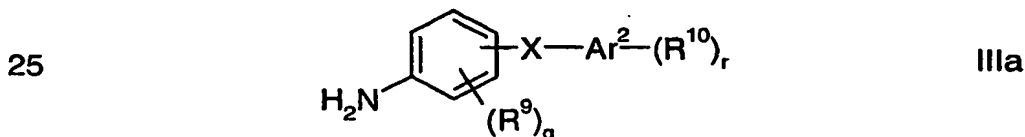
compound of formula IV and a compound of formula V is carried out in a polar reaction medium, for example in an acidic medium, for example in

acetic acid, preferably at lower temperatures, for example at temperatures between -20 and 50 °C, for example at about 0 °C or at about room temperature or in the range in between.

- 5 The transformation of a compound of formula VI into a compound of formula VII under solvolysing or preferably hydrolysed in conditions is advantageously carried out in an acidic or basic medium according to methods known per se. Preferably the transformation is carried out in a basic medium, for example in the presence of one or more bases,
- 10 preferably inorganic bases such as alkaline or alkaline-earth hydroxides, more preferably NaOH or KOH, in a preferably polar solvent such as water or alcohol, for example alcohols as described above/below, or mixtures thereof. Suitable reaction temperatures usually lie in the range between 0 °C and the boiling point of the solvent chosen and especially at about room
- 15 temperature. Preferably, the transformation under hydrolysing conditions is carried out in water/NaOH, preferably at lower temperatures, for example at temperatures between -20 and 50 °C, for example at about 0 °C.

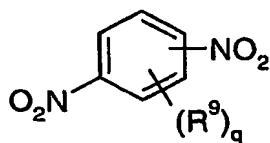
20 The compounds of formula III can be obtained according to methods known in the art.

If the compound of formula III is a compound according to formula IIIa,



it can be readily obtained in an advantageous manner by reacting a compound of formula VIIIa,

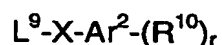
30



VIIIa

5 wherein R^9 and q are as defined above/below,

with a compound of formula IX,



IX

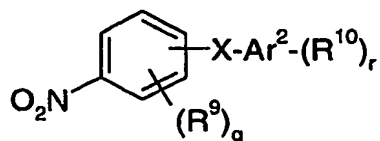
10

wherein L^9 is H or a metal ion, preferably a metal ion selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminum ions, especially preferred alkaline metal ions, of which Li, Na and K are especially preferred, and even more preferred is H; and Ar^2 , R^{10} ,
 15 r and X are as defined above/below, and more preferred wherein X is $(CHR^{11})_h-Q-(CHR^{12})_i$, wherein R^{11} , h , R^{12} and i are defined above/below, and preferably wherein h and/or i are 0, and especially Q is selected from a group consisting of O, S, $N-R^{17}$, $(CHR^{18}-O)_j$, $(CHR^{18}CHR^{19}-O)_j$, $CH=N-O$, $CH=N-NR^{17}$, SO_2NR^{17} , wherein j , R^{17} , R^{18} and R^{19} are as defined
 20 above/below;

optionally isolating the reaction product,

and transferring the obtained reaction product of formula XI

25



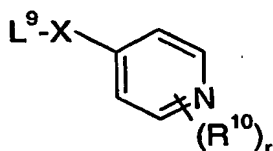
XI

30

into a compound of formula IIIa, preferably by hydrogenating the NO_2 -moiety of the compound of formula XI into a NH_2 -moiety. Methods

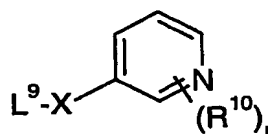
and reaction conditions for hydrogenating said NO₂-moiety into a NH₂-moiety are known in the art. In general, it is advantageous to carry out the hydrogenation reaction in a hydrogen atmosphere in the presence of a suitable catalyst, preferably a Palladium catalyst, for example Pd/C. In
 5 general, such hydrogenation reactions are carried out in a suitable solvent. Suitable solvents for hydrogenation reactions are known in the art. Suitable solvents, for example, are alcohols, especially methanol and ethanol and ethers, especially THF, and mixtures thereof. In general, the hydrogenation reactions are carried out at about normal pressure or slightly elevated
 10 pressure, for example between normal pressure and 3 bar pressure (about 300 kPa). The hydrogenation reaction is usually carried out in the temperature range between -20° and 150°, preferably between 0° and 50°.

Ar² is preferably pyridinyl. Accordingly, the compound of formula IX is
 15 preferably selected from the group consisting of formulae IXa and IXb,



20

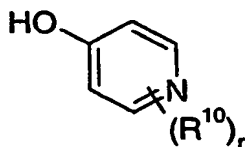
IXa



IXb

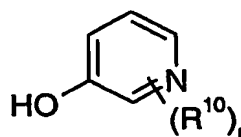
wherein L⁹, X, R¹⁰ and r are as defined above, and especially preferred from the group consisting of formulae IXc and IXd,

25



30

IXc



IXd

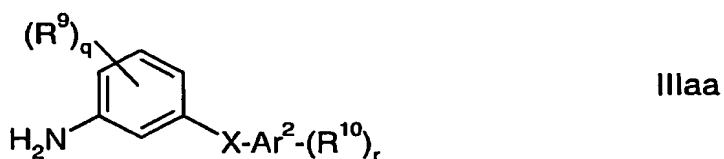
- 77 -

wherein R^{10} and r are as defined above, or the alkaline metal salts and especially the sodium or potassium salts thereof.

Accordingly, in formulae IIIa, IX, IXa, IXb and XI, the bridging group X is preferably O, S, OCH_2 and OCH_2CH_2 and especially is O.

In the formulae IX, IXa and IXb, L^8 is preferably H or selected from the group consisting of Na, K and Cs and especially preferred is H.

In general, this reaction is advantageous to produce compounds of formula IIIaa,



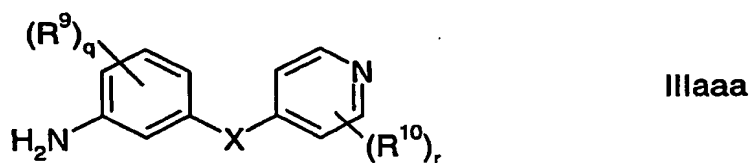
wherein R^9 , q , X , Ar^2 , R^{10} and r are as defined above/below.

To obtain compounds of formula IIIaa, it is reasonable to employ a compound of formula VIIIa that is selected from the compounds of formula VIIIa,



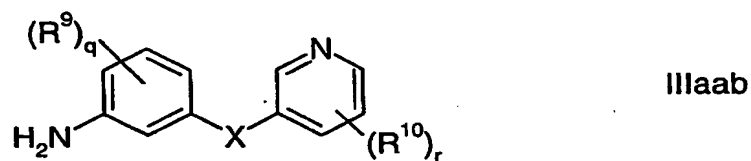
and proceed the reaction as described above/below.

Accordingly, by starting from a compound of formula VIIIa and a compound of formula IXa, the reaction preferably leads to compounds of formula IIIaaa,



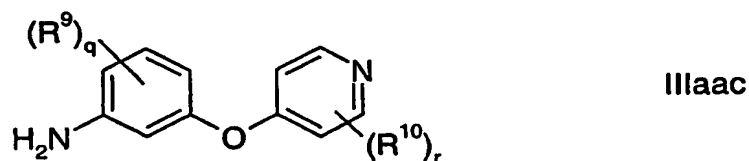
wherein R^9 , q , X , R^{10} and r are as defined above/below.

10 Accordingly, by starting from a compound of formula VIIIa and a compound of formula IXb, the reaction preferably leads to compounds of formula IIIaab,



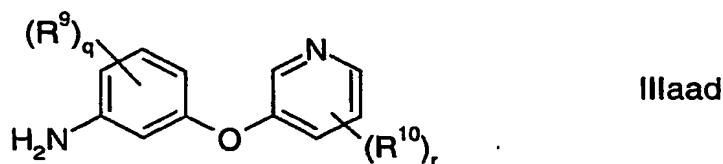
wherein R^9 , q , X , R^{10} and r are as defined above/below.

20 Accordingly, by starting from a compound of formula VIIIa and a compound of formula IXc, the reaction preferably leads to compounds of formula IIIaac,



wherein R^9 , q , R^{10} and r are as defined above/below.

30 Accordingly, by starting from a compound of formula VIIIa and a compound of formula IXd, the reaction preferably leads to compounds of formula



wherein R^9 , q , R^{10} and r are as defined above/below.

Some of the starting materials of the formula VIII and/or the formula IX are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

The reaction between the compound of formula VIII and IX is preferably carried out in the temperature range between 0° and 250° , more preferred room temperature and 200° , for example at about 120° , at about 150° or at about 180° . Reaction times depend on the respective reactants and the respective reaction temperature, but generally lie in the range between 30 min and 36 hrs, preferably 3 hrs and 24 hrs, more preferably 8 hrs and 20 hrs for example about 10 hrs, about 16 hrs or about 18 hrs.

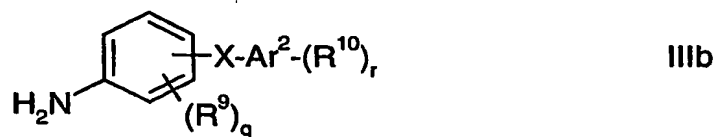
The reaction can be carried out in the absence of solvent or preferably in the presence of a solvent, preferable a solvent that is inert under the respective reaction conditions. Suitable inert solvents for carrying out the reaction are known in the art. Examples for suitable solvents are high boiling aliphatic hydrocarbons, high boiling aromatic carbons, for example toluene, xylenes, high boiling chlorinated hydrocarbons, such as trichloroethylene, tetrachloroethanes, pentachloroethanes and hexachloroethanes; high boiling ethers, such as ethylene glycol and propylene glycols; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); amides, such as acetamide, dimethylacetamide, dimethylformamide (DMF) or N-methyl pyrrolidone (NMP); sulfoxides, such as dimethyl sulfoxide (DMSO); or

mixtures of the said solvents. Preferred are amides, especially dimethylformamide (DMF).

Preferably, the reaction is carried out in the presence of a base. Suitable
 5 bases are known in the art. Preferred bases are organic bases and especially inorganic bases. Examples for inorganic bases are alkaline or alkaline-earth hydroxides, alkaline or alkaline-earth carbonates and alkaline or alkaline-earth bicarbonates or other salts of a weak acid and
 10 alkaline or alkaline-earth metals, preferably of potassium, sodium, calcium or cesium. Preferred inorganic bases are K_2CO_3 , Na_2CO_3 , $MgCO_3$, $CaCO_3$, $NaOH$ and KOH , especially preferred is K_2CO_3 . Examples for organic bases are triethyl amine, diisopropyl ethyl amine (DIPEA), dimethyl aniline, pyridine or chinoline. If an organic base is used, it is advantageous in
 15 general to use a base with a boiling point that is higher than the highest reaction temperature employed during the reaction.

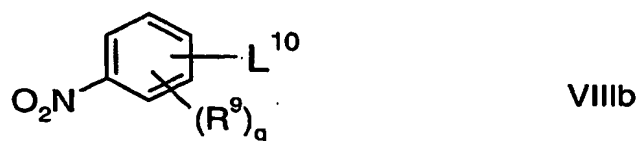
Alternatively, if the compound of formula III is a compound according to formula IIIb,

20



it can be readily obtained in an advantageous manner by reacting a
 25 compound of formula VIIIb,

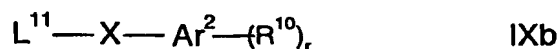
30



wherein R^9 and q are as defined above/below and wherein L^{10} is selected independently from the meanings given for L^1 . Preferably, L^{10} is halogen. More preferred, L^{10} is selected from the group consisting of Cl, Br and I. Especially preferred, L^{10} is Cl.

5

with a compound of formula IXb,



10

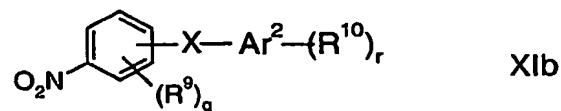
wherein L^{11} is H or a metal ion, preferably a metal ion, more preferred a metal ion selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and aluminium ions, especially preferred alkaline metal ions, of which Li, Na and K are especially preferred; and Ar^2 , R^{10} , r and X are as defined above/below, and especially wherein X is $(CHR^{11})_h-Q-(CHR^{12})_i$, $CH=N-O$, $CH=N-NR^{17}$, SO_2NR^{17} , wherein Q , R^{11} , R^{12} , h , i and R^{17} are as defined above/below;

15

optionally isolating the reaction product,

20

and transferring the obtained reaction product of formula XIb



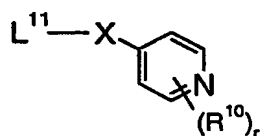
25

into a compound of formula IIIa, preferably by hydrogenating the NO_2 -moiety of the compound of formula XI into a NH_2 -moiety. Methods and reaction conditions for hydrogenating said NO_2 -moiety into a NH_2 -moiety are known in the art. In general, it is advantageous to carry out the hydrogenation reaction in a hydrogen atmosphere in the presence of a suitable catalyst, preferably a Palladium catalyst, for example Pd/C. In general, such hydrogenation reactions are carried out in a suitable solvent.

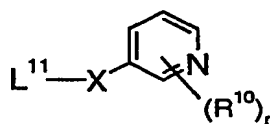
30

Suitable solvents for hydrogenation reactions are carried out in a suitable solvent. Suitable solvents for hydrogenation reactions are known in the art. Suitable solvents, for example, are alcohols, especially methanol and ethanol, ethers, especially THF, and mixtures thereof. In general, the hydrogenation reactions are carried out at about normal pressure or slightly elevated pressure, for example between normal pressure or slightly elevated pressure, for example between normal pressure and 3 bar pressure (about 300 kPa). The hydrogenation reaction is usually carried out in the temperature range between -20° and 150° , preferably 0° and 50° .

Ar^2 is preferably pyridinyl. Accordingly, the compound of formula IXb is preferably selected from the group consisting of formulae IXe and IXf,

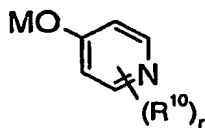


IXe

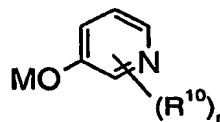


IXf

wherein L^{11} , X, R^{10} and r are as defined above, and especially preferred from the group consisting of formulae IXg and IXh,



IXg

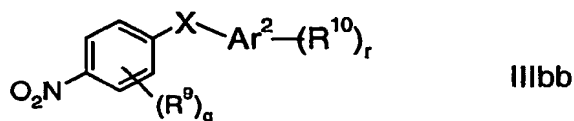


IXh

wherein R^{10} and r are as defined above, and wherein M is an alkaline metal ion and especially sodium or potassium, or the corresponding alcohols thereof.

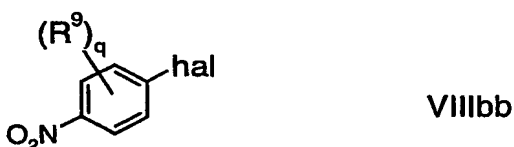
Accordingly, in formulae IIIb, IXb, IXe, IXf and Xlb, the bridging group X is preferably O, S, OCH₂ and OCH₂CH₂ and especially is O.

In general, this alternative reaction is advantageous to produce
5 compounds of formula IIIbb,



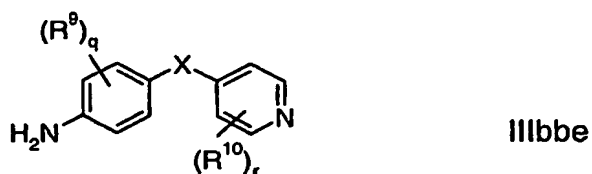
10 wherein R⁹, q, X, Ar², R¹⁰ and r are as defined above/below.

To obtain compounds of formula IIIbb, it is reasonable to employ a
compound of formula VIIIb that is selected from the compounds of formula
15 VIIIbb,



20 wherein hal is as defined above/below and especially is Cl, and proceed the alternative reaction as described above/below.

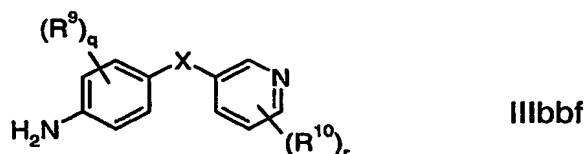
Accordingly, by starting from a compound a formula VIIIbb and a
25 compound of formula VIIIe, the reaction preferably leads to compounds of formula IIIbbe,



30

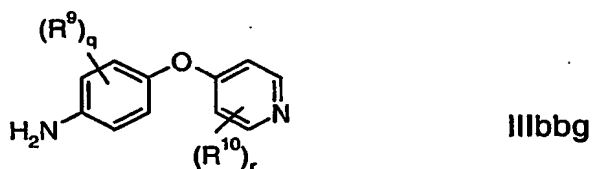
wherein R^9 , q , X , R^{10} and r are as defined above/below.

Accordingly, by starting from a compound of formula VIIIbb and a compound of formula IXf, the reaction preferably leads to compounds of formula IIIbbf,



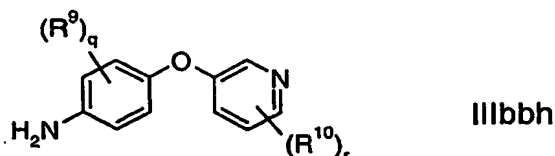
wherein R^9 , q , X , R^{10} and r are as defined above/below.

Accordingly, by starting from a compound of formula VIIIbb and a compound of formula IXg, the reaction preferably leads to compounds of formula IIIbbg,



wherein R^9 , q , R^{10} and r are as defined above/below.

Accordingly, by starting from a compound of formula VIIIb and a compound of formula IXh, the reaction preferably leads to compounds of formula IIIbbh,



wherein R^9 , q, R^{10} and r are as defined above/below.

Some of the starting materials of the formula VIIIb and/or the formula IXb are known and preferably commercially available. If they are not known,
5 they can be prepared by methods known per se.

The reaction between the compound of formula VIIIb and IXb is preferably carried out in the temperature range between 0° and 250°, more preferred 50° and 220°, for example at about 90°, at about 120°, at about 160°, at
10 about 180° or at about 200°. Reaction times depend on the respective reactants and the respective reaction temperature, but generally lie in the range between 10 min and 24 hrs, preferably 30 min and 12 hrs, more preferably 1 h and 6 hrs for example about 1,5 hrs, about 3 hrs, about 4 hrs or about 5 hrs.

15

The reaction can be carried out in the absence or the presence of a solvent, preferable a solvent that is inert under the respective reaction conditions. Suitable inert solvents for carrying out the reaction are known in the art. Examples for suitable solvents are aliphatic hydrocarbons,
20 aromatic carbons, for example toluene and xylenes, chlorinated hydrocarbons, such as dichloromethane, trichloromethane, trichloroethylene, tetrachloroethanes, pentachloroethanes and hexachloroethanes; ethers, such as diethylether, tert.-butyl methyl ether, ethylene glycol and propylene glycols; glycol ethers, such as ethylene
25 glycol monomethyl or monoethyl ether or ethylene glycol dimethyl ether (diglyme); nitriles, such as acetonitrile, amides such as acetamide, dimethylformamide (DMF) or N-methyl pyrrolidone (NMP); sulfoxides, such as dimethyl sulfoxide (DMSO); or mixtures of the said solvents.

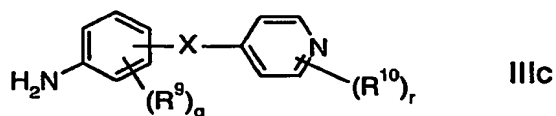
30

Preferably, the reaction is carried out in the presence of a catalyst. Suitable catalysts are known in the art. Preferred catalytic active metals and especially copper.

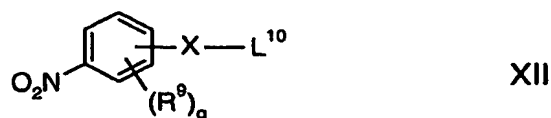
Preferably, the reaction is carried out by heating up a reaction mixture comprising one compound of formula VIIIb and one compound of formula IXb to a suitable reaction temperature, which preferably lies at the upper end of the given temperature ranges and more preferred is in the range
 5 between 150° and 200°, for example at about 180°, preferably in the presence of the suitable catalyst and especially in the presence of copper. Reaction times at this temperature are preferably as given above and especially in the range between 1 h and 5 hrs, for example about 3 hrs.
 10 Preferably, the reaction mixture is then allowed to cool down to a temperature in the lower range of the given temperature, more preferred to a temperature in the range between 50° and 150°, for example to about 90°. Preferably, a suitable solvent, especially tert.-butyl methyl ether, is then added and the reaction mixture is preferably kept at about the same
 15 temperature for some more time, preferably for 30 min to 2 hrs and more preferred for about one hour.

If the compound III is a compound according to formula IIIc,

20



it can be readily obtained in an advantageous manner by reacting a
 25 compound of formula XII



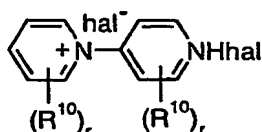
30

wherein L^{10} is H or a metal ion, preferably a metal ion selected from the group consisting of alkaline metal ions, alkaline-earth metal ions and

- 87 -

aluminium ions, especially preferred alkaline metal ions, of which Li, Na and K are especially preferred, and even more preferred is H; and R^9 , q and X are as defined above/below, and especially wherein X is $(CHR^{11})_h-Q-(CHR^{12})_i$, wherein R^{11} , h, R^{12} and i are defined above/below, and wherein h and/or i preferably are 0, and Q is selected from a group consisting of O, S, $N-R^{17}$, $(CHR^{18}-O)_j$, $(CHR^{18}CHR^{19}-O)_j$, $CH=N-O$, $CH=N-NR^{17}$, SO_2NR^{17} , wherein j, R^{17} , R^{18} and R^{19} are as defined above/below;

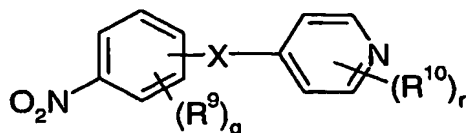
with a compound of formula XIII,



XIII

wherein hal is independently selected from the group consisting of Cl, Br and I, the residue R^{10} are the same or different and have the meanings given above/below and preferably have both the same meaning, and the indices r are the same or different and have the meanings given above/below and preferably are the same,

optionally isolating the reaction product, and transferring the obtained reaction product of formula XIV



XIV

into a compound of formula IIIc, preferably by hydrogenating the NO_2 -moiety of the compound of formula XIV into a NH_2 -moiety, for example as described above for the compound of formula XI.

In the compounds IIIc, XIII and XIV, r is preferably in each case identical and even more preferred in each case 0.

5 In formulae IIIc, XII and XIV, the bridging group X is preferably O, S, OCH₂ and OCH₂CH₂ and especially is O.

In the formula XII, L¹⁰ is preferably H or selected from the group consisting of Na and K and especially preferred is H.

10 The reaction between the compound of formula XII and XIII is preferably carried out in the temperature range between 0° and 250°, more preferred between room temperature and 200°, for example at about 120°, at about 150° or at about 180°. Reaction times depend on the respective reactants and the respective reaction temperature, but generally lie in the range
15 between 30 min and 24 hrs, preferably one hour and 12 hrs, for example about 2 hrs, about 3 hrs or about 6 hrs. The reaction can be carried out in the absence of solvent or in the presence of a solvent, preferable a solvent that is inert under the respective reaction conditions. Suitable inert solvents for carrying out the reaction are known in the art.

20 Some of the starting materials of the formula XII and/or the formula XIII are known and preferably commercially available. If they are not known, they can be prepared by methods known per se.

25 Independently of the chosen reaction route, it is in many cases possible or even feasible to introduce residues R⁸, R⁹ and/or R¹⁰ into one or more of the compounds described above, or, if the compound already comprises one or more residues R⁸, R⁹ and/or R¹⁰, to introduce additional residues R⁸, R⁹ and/or R¹⁰ into said compound. The introduction of additional
30 residues can be readily performed by methods known in the art and especially by aromatic substitution, for example nucleophilic aromatic substitution or electrophilic aromatic substitution. For example, in

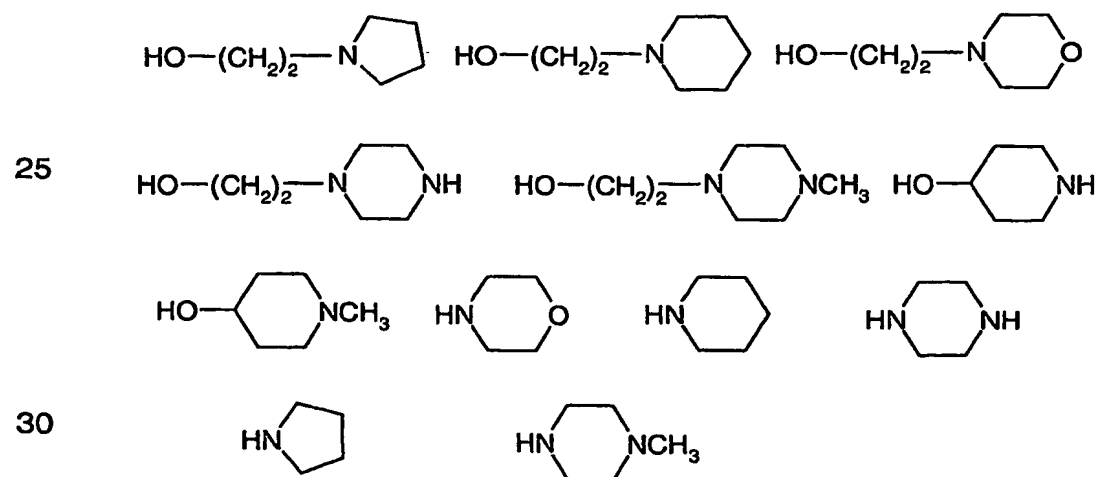
compounds, wherein the benzimidazole-moiety and/or Ar^2 comprise one or more halogen and preferably fluorine substituents, one or more of the halogen/fluorine substituents can be easily substituted by hydroxy, thio and/or amino substituted hydrocarbons, preferably selected from the group

5 consisting of $\text{HO}(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $\text{HO}(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $\text{HO}(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{OR}^{12}$, $\text{HO}(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $\text{HO}(\text{CH}_2)_n\text{COOR}^{13}$, $\text{HO}(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$ $\text{HNR}^{11}(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $\text{HNR}^{11}(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $\text{HNR}^{11}(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{OR}^{12}$, $\text{HNR}^{11}(\text{CH}_2)_n\text{NR}^{11}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $\text{HNR}^{11}(\text{CH}_2)_n\text{COOR}^{13}$ and

10 $\text{HNR}^{11}(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$ wherein R^{11} , R^{12} and R^{13} are defined as above and n is as defined above, preferably n is 0, 1 or 2 and especially is 0, k is 1 to 4 and preferably 1 or 2, and u is preferably 2. In this embodiment R^{11} , R^{12} and R^{13} are more preferably selected independently from each other from the group consisting of H, methyl and ethyl. Even more preferred, the

15 hydroxy, thio and/or amino substituted hydrocarbons are selected from the group consisting of NH_3 , $\text{HN}(\text{CH}_3)_2$, NH_2CH_3 , $\text{HN}(\text{C}_2\text{H}_5)_2$, $\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$, $\text{HOCH}_2\text{CH}_2\text{NH}_2$, $\text{HOCH}_2\text{CH}_2\text{NHCH}_3$, $\text{HN}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{NH}_2$, $\text{HN}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $\text{HN}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{OCH}_3$, $\text{HOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $\text{HOCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$,

20 HSCH_3 , HSC_2H_5 , and compounds of the formulae



or salts and especially metal salts thereof.

On the other hand, it is in many cases possible or even feasible to modify or derivatize one or more of the residue is R^8 , R^9 and R^{10} into residues R^8 , R^9 and/or R^{10} other than the ones originally present. For example, CH_3 -groups can be oxidised into aldehyde groups or carbonic acid groups, thio atom containing groups, for example S-alkyl or S-aryl groups, can be oxidised into SO_2 -alkyl or SO_2 -aryl groups, respectively, carbonic acid groups can be derivatized to carbonic acid ester groups or carbon amide groups and carbonic acid ester groups or carbon amide groups can be hydrolysed into the corresponding carbonic acid groups. Methods for performing such modifications or derivatizations are known in the art, for example from Houben-Weyl, Methods of Organic Chemistry.

Every reaction step described herein can optionally be followed by one or more working up procedures and/or isolating procedures. Suitable such procedures are known in the art, for example from standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart). Examples for such procedures include, but are not limited to evaporating a solvent, distilling, crystallization, fractionised crystallization, extraction procedures, washing procedures, digesting procedures, filtration procedures, chromatography, chromatography by HPLC and drying procedures, especially drying procedures in vacuo and/or elevated temperature.

A base of the formula I can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in a preferably inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, sulfurous acid, dithionic acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid,

phosphoric acids, such as, for example, orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, 5 hexanoic acid, octanoic acid, decanoic acid, hexadecanoic acid, octadecanoic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2- 10 hydroxyethanesulfonic acid, benzenesulfonic acid, trimethoxybenzoic acid, adamantanecarboxylic acid, p-toluenesulfonic acid, glycolic acid, embonic acid, chlorophenoxyacetic acid, aspartic acid, glutamic acid, proline, glyoxylic acid, palmitic acid, parachlorophenoxyisobutyric acid, cyclohexanecarboxylic acid, glucose 1-phosphate, naphthalenemono- and 15 -disulfonic acids or laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used to isolate and/or purify the compounds of the formula I. On the other hand, compounds of the formula I can be converted into the corresponding metal salts, in particular alkali metal salts or alkaline earth metal salts, or into the 20 corresponding ammonium salts, using bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate). Suitable salts are furthermore substituted ammonium salts, for example the dimethyl-, diethyl- and diisopropylammonium salts, monoethanol-, diethanol- and diisopropanolammonium salts, cyclohexyl- 25 and dicyclohexylammonium salts, dibenzylethylenediammonium salts, furthermore, for example, salts with arginine or lysine.

On the other hand, if desired, the free bases of the formula I can be liberated from their salts using bases (for example sodium hydroxide, 30 potassium hydroxide, sodium carbonate or potassium carbonate).

The invention relates to compounds of the formula I and physiologically acceptable salts and solvates thereof as medicaments.

5 The invention also relates to the compounds for the formula I and physiologically acceptable salts and solvates thereof as kinase inhibitors.

10 The invention furthermore relates to the use of the compounds of the formula I and/or physiologically acceptable salts and/or solvates thereof for the preparation of pharmaceutical compositions and/or pharmaceutical preparations, in particular by non-chemical methods. The invention furthermore relates to the use of the compounds of the formula I and/or physiologically acceptable salts and/or solvates thereof for the preparation of pharmaceutical compositions and/or pharmaceutical preparations, in particular by non-chemical methods. In this cases, one or more
15 compounds according to the invention can be converted into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or adjuvant and, if desired, in combination with one or more further active ingredients.

20 The invention further relates to the use of one or more of the compounds according to the invention, selected from the group consisting of compounds of the formula I as free bases, pharmaceutically acceptable derivatives, preferably solvates of compounds of the formula I and salts of compounds of formula I, for the production of pharmaceutical
25 compositions and/or pharmaceutical preparations, in particular by a non-chemical route. In general, non-chemical routes for the production of pharmaceutical compositions and/or pharmaceutical preparations comprise processing steps on suitable mechanical means known in the art that transfer one or more compounds according to the invention into a
30 dosage form suitable for administration to a patient in need of such a treatment. Usually, the transfer of one or more compounds according to the invention into such a dosage form comprises the addition of one or

more compounds, selected from the group consisting of carriers, excipients, auxiliaries and pharmaceutical active ingredients other than the compounds according to the invention. Suitable processing steps include, but are not limited to combining, milling, mixing, granulating, dissolving, dispersing, homogenizing, casting and/or compressing the respective active and non-active ingredients. In this respect, active ingredients are preferably at least one compound according to this invention and one or more additional compounds other than the compounds according to the invention, which show valuable pharmaceutical properties, preferably those pharmaceutical active agents other than the compounds according to the invention which are disclosed herein.

The process for preparing pharmaceutical compositions and/or pharmaceutical preparations preferably comprises one or more processing steps, selected from the group consisting of combining, milling, mixing, granulating, dissolving, dispersing, homogenizing and compressing. The one or more processing steps are preferably performed on one or more of the ingredients which are to form the pharmaceutical composition and/or pharmaceutical preparation preferably according to the invention. Even more preferred, said processing steps are performed on two or more of the ingredients which are to form the pharmaceutical composition and/or pharmaceutical preparation, said ingredients comprising one or more compounds according to the invention and, additionally, one or more compounds, preferably selected from the group consisting of active ingredients other than the compounds according to the invention, excipients, auxiliaries, adjuvants and carriers. Mechanical means for performing said processing steps are known in the art, for example from Ullmann's Encyclopedia of Industrial Chemistry, 5th Edition.

Preferably, one or more compounds according to the invention are converted into a suitable dosage form together with at least one compound selected from the group consisting of excipients, auxiliaries, adjuvants and

carriers, especially solid, liquid and/or semi-liquid excipients, auxiliaries, adjuvants and carriers, and, if desired, in combination with one or more further active ingredients.

5 Suitable dosage forms include, but are not limited to tablets, capsules, semi-solids, suppositories, aerosols, which can be produced according to methods known in the art, for example as described below:

10 tablets mixing of active ingredient/s and auxiliaries, compression of said mixture into tablets (direct compression), optionally granulation of part of mixture before compression

15 capsules mixing of active ingredient/s and auxiliaries to obtain a flowable powder, optionally granulating powder, filling powders/granulate into opened capsules, capping of capsules

20 semi-solids (ointments, gels, creams) dissolving/dispersing active ingredient/s in an aqueous or fatty carrier; subsequent mixing of aqueous/fatty phase with complementary fatty resp. aqueous phase, homogenisation (creams only)

25 suppositories (rectal and vaginal) dissolving/dispersing active ingredient/s in carrier material liquified by heat (rectal: carrier material normally a wax; vaginal: carrier normally a heated solution of a gelling agent), casting said mixture into suppository forms, annealing and withdrawal suppositories from the forms

30

aerosols: dispersing/dissolving active agent/s in a propellant, bottling said mixture into an atomizer

5

The invention thus relates to pharmaceutical compositions and/or pharmaceutical preparations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts and/or solvates and especially to pharmaceutical compositions and/or pharmaceutical preparations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts and/or solvates.

10

Preferably, the pharmaceutical compositions and/or pharmaceutical preparations according to the invention contain a therapeutic effective amount of one or more compounds according to the invention. Said therapeutic effective amount of one or more of the compounds according to the invention is known to the skilled artisan or can be easily determined by standard methods known in the art. For example, the compounds according to the invention can be administered to a patient in an analogous manner to other compounds that are effective as raf-kinase inhibitors, especially in an analogous manner to the compounds described in WO 00/42012 (Bayer). Usually, suitable doses that are therapeutically effective lie in the range between 0.0005 mg and 1000 mg, preferably between 0.005 mg and 500 mg and especially between 0.5 and 100 mg per dose unit. The daily dose comprises preferably more than 0.001 mg, more preferred more than 0.01 milligram, even more preferred more than 0.1 mg and especially more than 1.0 mg, for example more than 2.0 mg, more than 5 mg, more than 10 mg, more than 20 mg, more than 50 mg or more than 100 mg, and preferably less than 1500 mg, more preferred less than 750 mg, even more preferred less than 500 mg, for example less than 400 mg, less than 250 mg, less than 150 mg, less than 100 mg, less than 50 mg or less than 10 mg.

20

25

30

The specific dose for the individual patient depends, however, on the multitude of factors, for example on the efficacy of the specific compounds employed, on the age, body weight, general state of health, the sex, the
5 kind of diet, on the time and route of administration, on the excretion rate, the kind of administration and the dosage form to be administered, the pharmaceutical combination and severity of the particular disorder to which the therapy relates. The specific therapeutic effective dose for the individual patient can readily be determined by routine experimentation, for
10 example by the doctor or physician which advises or attends the therapeutic treatment.

However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed,
15 on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the rate of excretion, medicament combination and severity of the particular illness to which the therapy applies. Parenteral administration is preferred. Oral administration is especially preferred.

20 These compositions and/or preparations can be used as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the novel compounds, for
25 example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc or vaseline. Examples for suitable dosage forms, which are especially suitable for oral administration are, in particular, tablets, pills, coated tablets, capsules, powders,
30 granules, syrups, juices or drops. Further examples for suitable dosage forms, which are especially suitable for rectal administration are suppositories, further examples for suitable dosage forms, which are

especially suitable for parenteral administration are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical application are ointments, creams or powders. The novel compounds may also be lyophilised and the resulting lyophilisates used, for example, for the preparation of injection preparations. The compositions and/or preparations indicated may be sterilized and/or comprise assistants, such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, dyes and flavors and/or one or more further active ingredients, for example one or more vitamins.

For administration as an inhalation spray, it is possible to use sprays in which the active ingredient is either dissolved or suspended in a propellant gas or propellant gas mixture (for example CO₂ or chlorofluorocarbons). The active ingredient is advantageously used here in micronized form, in which case one or more additional physiologically acceptable solvents may be present, for example ethanol. Inhalation solutions can be administered with the aid of conventional inhalers.

The compounds of the formula I and their physiologically acceptable salts and solvates and especially the compounds of formula I and their physiologically acceptable salts and solvates can be employed for combating one or more diseases, for example allergic diseases, psoriasis and other skin diseases, especially melanoma, autoimmune diseases, such as, for example, rheumatoid arthritis, multiple sclerosis, Crohn's disease, diabetes mellitus or ulcerative colitis.

In general, the substances according to the invention are preferably administered in doses corresponding to the compound rolipram of between 1 and 500 mg, in particular between 5 and 100 mg per dosage unit. The daily dose is preferably between about 0.02 and 10 mg/kg of body weight. However, the specific dose for each patient depends on a wide variety of

5 factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the excretion rate, medicament combination and severity of the particular illness to which the therapy applies.

10 The compounds of the formula I according to claim 1 and/or their physiologically acceptable salts are also used in pathological processes which are maintained or propagated by angiogenesis, in particular in tumours, restenoses, diabetic retinopathy, macular degenerative disease or rheumatoid arthritis.

15 Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms and the susceptibility of the subject to side effects. Some of the specific compounds are more potent than others. Preferred dosages for a given compound are readily determinable by those of skill in the art by a variety of means. A preferred means is to measure the physiological potency of a given compound.

20 For use in the subject methods, the subject compounds may be formulated with pharmaceutically active agents other than the compounds according to the invention, particularly other anti-metastatic, antitumor or anti-angiogenic agents. Angiostatic compounds of interest include angiostatin, enclostatin, carboxy terminal peptides of collagen alpha (XV), etc.

25 Cytotoxic and cytostatic agents of interest include adriamycin, aleran, Ara-C, BICNU, busulfan, CNNU, cisplatin, cytoxan, daunorubicin, DTIC, 5-FU, hydrea, ifosfamide, methotrexate, mithramycin, mitomycin, mitoxantrone, nitrogen mustard, velban, vincristine, vinblastine, VP-16,

30 carboplatin, fludarabine, gemcitabine, idarubicin, irinotecan, leustatin, navelbine, taxol, taxotere, topotecan, etc.

The compounds of the invention preferably show antiproliferative effects, for example in an in vivo xenograft tumor model. The subject compounds can be administered to a subject having a hyperproliferative disorders, e.g., to inhibit tumor growth, to decrease inflammation associated with a lymphoproliferative disorder, to inhibit graft rejection, or neurological damage due to tissue repair, etc. The present compounds can be useful for prophylactic or therapeutic purposes. As used herein, the term "treating" is used to refer to both prevention of disease, and treatment of pre-existing conditions. The prevention of proliferation is accomplished by administration of the subject compounds prior to development of overt disease, e.g., to prevent the regrowth of tumors, prevent metastatic growth, diminish restenosis associated with cardiovascular surgery, etc. Alternatively the compounds are used to treat ongoing disease, by stabilizing or improving the clinical symptoms of the patient.

15

Furthermore, the compounds according the invention preferably can be utilized in the treatment of infectious diseases of diverse genesis.

20

Infections according the invention include, but are not limited to infections caused by pathogenic microorganisms, such as bacteria, fungi, viruses and protozoans, for example influenza (Pleschka, S. et al. *Nature Cell Biol.* 2001, 3, page 301-305), retroviruses, for example HIV infection (Yang, X. et al. *J. Biol. Chem.* 1999, 274, page 27981-27988; Popik, W et al *Mol Cel Biol.* 1996, 16, page 6532-6541), Hepatitis B (Benn, J et al., *Proc. Natl. Acad. Sci.* 1995, 92, page 11215-11219), Hepatitis C (Aoki et al. *J. Virol.* 2000, 74, page 1736-1741), papillomavirus, parainfluenza, rhinoviruses, adenoviruses, *Helicobacter pylori*, and viral and bacterial infections of the skin (e.g. cold sores, warts, chickenpox, molluscum. contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, Athlete's foot and ringworm).

30

Furthermore, the compounds according the invention preferably show anti-angiogenic properties.

Thus, compounds of the present invention can be advantageously employed in the treatment of one or more diseases afflicting mammals which are characterized by cellular proliferation in the area of disorders associated with neo-vascularization and/or vascular permeability including blood vessel proliferative disorders including arthritis and restenosis; fibrotic disorders including hepatic cirrhosis and atherosclerosis; mesangial cell proliferative disorders include glomerulonephritis, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection and glomerulopathies; and metabolic disorders include psoriasis, diabetes mellitus, chronic wound healing, inflammation and neurodegenerative diseases.

The host, or patient, may be from any mammalian species, e.g., primate sp., particularly human; rodents, including mice, rats and hamsters; rabbits; equines, bovines, canines, felines; etc. Animal models are of interest for experimental investigations, providing a model for treatment of human disease.

The susceptibility of a particular cell to treatment with the subject compounds may be determined by in vitro testing. Typically a culture of the cell is combined with a subject compound at varying concentrations for a period of time sufficient to allow the active agents to induce cell death or inhibit migration, usually between about one hour and one week. For in vitro testing, cultured cells from a biopsy sample may be used. The viable cells left after treatment are then counted.

The dose will vary depending on the specific compound utilized, specific disorder, patient status, etc. Typically a therapeutic dose will be sufficient to substantially decrease the undesirable cell population in the targeted

tissue, while maintaining patient viability. Treatment will generally be continued until there is a substantial reduction, e.g., at least about 50 %, decrease in the cell burden, and may be continued until there are essentially none of the undesirable cells detected in the body.

5

The compounds according to the invention are preferably administered to human or nonhuman animals, more preferred to mammalian animals and especially to humans.

10

The compounds also find use in the specific inhibition of a signaling pathway mediated by protein kinases. Protein kinases are involved in signaling pathways for such important cellular activities as responses to extracellular signals and cell cycle checkpoints. Inhibition of specific protein kinases provided a means of intervening in these signaling

15

pathways, for example to block the effect of an extracellular signal, to release a cell from cell cycle checkpoint, etc. Defects in the activity of protein kinases are associated with a variety of pathological or clinical conditions, where there is a defect in the signaling mediated by protein kinases. Such conditions include those associated with defects in cell cycle

20

regulation or in response to extracellular signals, e.g., immunological disorders, autoimmune and immunodeficiency diseases; hyperproliferative disorders, which may include psoriasis, arthritis, inflammation,

endometriosis, scarring, cancer, etc. The compounds of the present invention are active in inhibiting purified kinase proteins preferably raf

25

kinases, e.g., there is a decrease in the phosphorylation of a specific substrate in the presence of the compound. The compounds of the invention may also be useful as reagents for studying signal transduction or any of the clinical disorders listed throughout this application.

30

There are many disorders associated with a dysregulation of cellular proliferation. The conditions of interest include, but are not limited to, the following conditions. The subject compounds are useful in the treatment of

a variety of conditions where there is proliferation and/or migration of smooth muscle cells, and/or inflammatory cells into the intimal layer of a vessel, resulting in restricted blood flow through that vessel, e.g., neointimal occlusive lesions. Occlusive vascular conditions of interest
5 include atherosclerosis, graft coronary vascular disease after transplantation, vein graft stenosis, peri-anastomatic prosthetic graft stenosis, restenosis after angioplasty or stent placement, and the like.

Diseases where there is hyperproliferation and tissue remodelling or repair
10 or reproductive tissue, e.g., uterine, testicular and ovarian carcinomas, endometriosis, squamous and glandular epithelial carcinomas of the cervix, etc. are reduced in cell number by administration of the subject compounds. The growth and proliferation of neural cells is also of interest.

15 Tumor cells are characterized by uncontrolled growth, invasion to surrounding tissues, and metastatic spread to distant sites. Growth and expansion requires an ability not only to proliferate, but also to down-modulate cell death (apoptosis) and activate angiogenesis to produce a tumor neovasculature.

20 Tumors of interest for treatment include carcinomas, e.g., colon, duodenal, prostate, breast, melanoma, ductal, hepatic, pancreatic, renal, endometrial, stomach, dysplastic oral mucosa, polyposis, invasive oral cancer, non-small cell lung carcinoma, transitional and squamous cell
25 urinary carcinoma etc.; neurological malignancies; e.g. neuroblastoma, gliomas, etc.; hematological malignancies, e.g., childhood acute leukaemia, non-Hodgkin's lymphomas, chronic lymphocytic leukaemia, malignant cutaneous T-cells, mycosis fungoides, non-MF cutaneous T-cell-lymphoma, lymphomatoid papulosis, T-cell rich cutaneous lymphoid
30 hyperplasia, bullous pemphigoid, discoid lupus erythematosus, lichen planus, etc.; and the like.

Tumors of neural tissue are of particular interest, e.g., gliomas, neuromas, etc. Some cancers of particular interest include breast cancers, which are primarily adenocarcinoma subtypes. Ductal carcinoma in situ is the most common type of noninvasive breast cancer. In DCIS, the malignant cells have not metastasized through the walls of the ducts into the fatty tissue of the breast. Infiltration (or invasive) ductal carcinoma (IDC) has metastasized through the wall of the duct and invaded the fatty tissue of the breast. Infiltrating (or invasive) lobular carcinoma (ILC) is similar to IDC, in that it has the potential to metastasize elsewhere in the body. About 10 % to 15 % of invasive breast cancers are invasive lobular carcinomas.

Also of interest is non-small cell lung carcinoma. Non-small cell lung cancer (NSCLC) is made up of three general subtypes of lung cancer. Epidermoid carcinoma (also called squamous cell carcinoma) usually starts in one of the larger bronchial tubes and grows relatively slowly. The size of these tumors can range from very small to quite large. Adenocarcinoma starts growing near the outside surface of the lung and may vary in both size and growth rate. Some slowly growing adenocarcinomas are described as alveolar cell cancer. Large cell carcinoma starts near the surface of the lung, grows rapidly, and the growth is usually fairly large when diagnosed. Other less common forms of lung cancer are carcinoid, cylindroma, mucoepidermoid, and malignant mesothelioma.

Melanoma is a malignant tumor of melanocytes. Although most melanomas arise in the skin, they also may arise from mucosal surfaces or at other sites to which neural crest cells migrate. Melanoma occurs predominantly in adults, and more than half of the cases arise in apparently normal areas of the skin. Prognosis is affected by clinical and histological factors and by anatomic location of the lesion. Thickness and/or level of invasion of the melanoma, mitotic index, tumor infiltrating lymphocytes, and ulceration or bleeding at the primary site affect the

prognosis. Clinical staging is based on whether the tumor has spread to regional lymph nodes or distant sites. For disease clinically confined to the primary site, the greater the thickness and depth of local invasion of the melanoma, the higher the chance of lymph node metastases and the worse the prognosis. Melanoma can spread by local extension (through lymphatics) and/or by hematogenous routes to distant sites. Any organ may be involved by metastases, but lungs and liver are common sites.

Other hyperproliferative diseases of interest relate to epidermal hyperproliferation, tissue, remodeling and repair. For example, the chronic skin inflammation of psoriasis is associated with hyperplastic epidermal keratinocytes as well as infiltrating mononuclear cells, including CD4+ memory T cells, neutrophils and macrophages.

The proliferation of immune cells is associated with a number of autoimmune and lymphoproliferative disorders. Diseases of interest include multiple sclerosis, rheumatoid arthritis and insulin dependent diabetes mellitus. Evidence suggests that abnormalities in apoptosis play a part in the pathogenesis of systemic lupus erythematosus (SLE). Other lymphoproliferative conditions the inherited disorder of lymphocyte apoptosis, which is an autoimmune lymphoproliferative syndrome, as well as a number of leukemia's and lymphomas. Symptoms of allergies to environmental and food agents, as well as inflammatory bowel disease, may also be alleviated by the compounds of the invention.

Surprisingly, it has been found that benzimidazole carboxamides according to the invention are able to interact with signaling pathways, especially the signaling pathways described herein and preferably the raf-kinase signaling pathway. Benzimidazole carboxamides according to the invention preferably show advantageous biological activity which can easily be demonstrated according to methods known in the art, for example by enzyme based assays. Suitable assays are known in the art, for example

from the literature cited herein and the references cited in the literature, or can be developed and/or performed in an analogous manner thereof. In such enzyme based assays, benzimidazole carboxamides according to invention show an effect, preferably a modulating and especially an inhibiting effect which is usually documented by IC_{50} values in a suitable range, preferably in the micromolar range and more preferred in the nanomolar range.

In general, compounds according to the invention are to be regarded as suitable kinase-modulators and especially suitable kinase-inhibitors according to the invention if they show an effect or an activity to one or more kinases, preferably to one or more raf-kinases that preferably lies, determined as IC_{50} -value, in the range of 100 μmol or below, preferably 10 μmol or below, more preferably in the range of 3 μmol or below, even more preferably in the range of 1 μmol or below and most preferably in the nanomolar range. Especially preferred for use according to the invention are kinase-inhibitors as defined above/below, that show an activity, determined as IC_{50} -value, to one or more raf-kinases, preferably including A-raf, B-raf and c-raf1 or consisting of A-raf, B-raf and c-raf1 and more preferred including c-raf1 or consisting of c-raf1, in the range of 0.5 μmol or below and especially in the range of 0.1 μmol or below. In many cases an IC_{50} -value at the lower end of the given ranges is advantageous and in some cases it is highly desirable that the IC_{50} -value is as small as possible or the IC_{50} -values are as small as possible, but in general IC_{50} -values that lie between the above given upper limits and a lower limit in the range of 0.0001 μmol , 0.001 μmol , 0.01 μmol or even above 0.1 μmol are sufficient to indicate the desired pharmaceutical activity. However, the activities measured can vary depending on the respective testing system or assay chosen.

30

As discussed herein, these signaling pathways are relevant for various disorders. Accordingly, by interacting with one or more of said signaling

pathways, benzimidazole carboxamides are useful in the prevention and/or the treatment of disorders that are dependent from said signaling pathways.

- 5 Subject of the present invention are therefore benzimidazole carboxamides according to the invention as promoters or inhibitors, preferably as inhibitors, of the signaling pathways described herein. Preferred subject of the invention are therefore benzimidazole carboxamides according to the invention as promoters or inhibitors,
- 10 preferably as inhibitors of the raf-kinase pathway. More preferred subject of the invention are therefore benzimidazole carboxamides according to the invention as promoters or inhibitors, preferably as inhibitors of the raf-kinase. Even more preferred subject of the invention are benzimidazole carboxamides according to the invention as promoters or inhibitors,
- 15 preferably as inhibitors of one or more raf-kinases, selected from the group consisting of A-raf, B-raf and c-raf1. Especially preferred subject of the invention are benzimidazole carboxamides according to the invention as promoters or inhibitors, preferably as inhibitors of c-raf1.
- 20 Thus, subject of the present invention are benzimidazole carboxamides according to the invention as medicaments. Subject of the present invention are benzimidazole carboxamides according to the invention as medicament active ingredients. Further subject of the present invention is the use of one or more benzimidazole carboxamides according to the
- 25 invention as a pharmaceutical. Further subject of the present invention is the use of one or more benzimidazole carboxamides according to the invention in the treatment and/or the prophylaxis of disorders, preferably the disorders described herein, more preferred disorders that are caused, mediated and/ or propagated by signalling pathways discussed herein,
- 30 even more preferred disorders that are caused, mediated and/or propagated by raf-kinases and especially disorders that are caused, mediated and/or propagated by raf-kinases, selected from the group

consisting of A-raf, B-raf and c-raf1. Usually, the disorders discussed herein are divided into two groups, hyperproliferative and non hyperproliferative disorders. In this context, infection or infectious diseases, psoriasis, arthritis, inflammation, endometriosis, scarring, benign
5 prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases are to be regarded as noncancerous disorders, of which infection, arthritis, inflammation, immunological diseases, autoimmune diseases and immunodeficiency diseases are usually regarded as non hyperproliferative disorders. In this context, brain
10 cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia are to be regarded as cancerous disorders, all of which are usually
15 regarded as hyperproliferative disorders. Especially cancerous cell growth and especially cancerous cell growth mediated by raf-kinase is a disorder which is a target of the present invention. Subject of the present invention therefore are benzimidazole carboxamides according to the invention as medicaments and/or medicament active ingredients in the treatment
20 and/or the prophylaxis of said disorders and the use of benzimidazole carboxamides according to the invention for the manufacture of a pharmaceutical for the treatment and/or the prophylaxis of said disorders as well as a method of treatment of said disorders, comprising administering one or more benzimidazole carboxamides according to the
25 invention to a patient in need of such an administration.

Accordingly, subject of the present invention are pharmaceutical compositions that contain one or more benzimidazole carboxamides according to the invention. Subject of the present invention are especially
30 pharmaceutical compositions that contain one or more benzimidazole carboxamides according to the invention and one or more additional

compounds (other than the compounds of the instant invention), preferably selected from the group consisting of physiologically acceptable excipients, auxiliaries, adjuvants, carriers and pharmaceutically active ingredients other than the compounds according to the invention.

5 Accordingly, subject of the present invention is a process for the manufacture of a pharmaceutical composition, wherein one or more benzimidazole carboxamides according to the invention and one or more compounds (other than the compounds of the instant invention), preferably selected from the group consisting of carriers, excipients, auxiliaries,
10 adjuvants and pharmaceutically active ingredients other than the compounds according to the invention.

Accordingly, the use of the compounds according to the invention in the treatment of hyperproliferative disorders is a subject of the instant
15 invention.

Accordingly, the use of the compounds according to the invention for producing a medicament for the treatment of hyperproliferative disorders is a subject of the instant invention.

20 Above and below, all temperatures are given in °C. In the examples below, "conventional work-up" means that the organic phase is washed with saturated NaHCO₃ solution, if desired with water and saturated NaCl solution, the phases are separated, the organic phase is dried over sodium
25 sulfate and evaporated, and the product is purified by chromatography on silica gel, by preparative HPLC and/or by crystallization.

The present invention relates to benzimidazole carboxamides of formula I, the use of the compounds of formula I as inhibitors of raf-kinase, the use
30 of the compounds of formula I for the manufacture of a pharmaceutical composition and a method of treatment, comprising administering said pharmaceutical composition to a patient.

Synthesis of the phenylamine moieties

10

Reaction scheme showing the synthesis of compound 2:

4-nitrophenol reacts with a pyridine-based salt (containing a quaternary nitrogen and a bromide counterion) at 150 °C to form intermediate 1 (4-(2-pyridin-2-yloxy)benzenesulfonate).

Intermediate 1 is then reduced using Pd/C and H₂ in MeOH to yield compound 2 (4-(2-pyridin-2-yloxy)aniline).

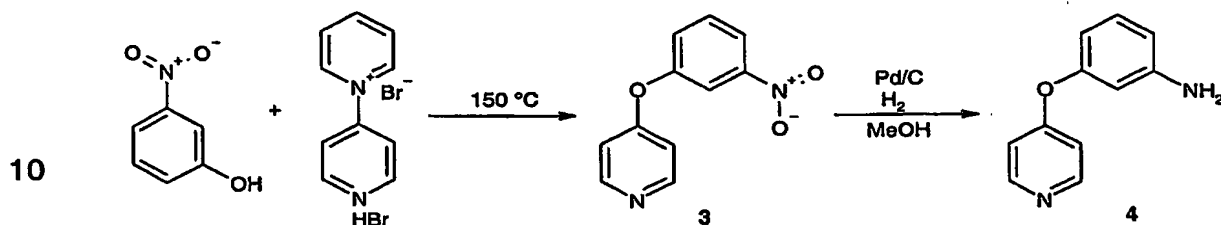
25 Yield: 75 g (25%) of **1**, brown crystals

30 b) Compound 1 was hydrogenated at room temperature using Pd/C in MeOH. The reaction solution was filtered through kieselguhr and rinsed with MeOH, and the filtrate was subsequently evaporated. The residue was digested with diethyl ether:petroleum ether = 2:1, filtered off with

suction, rinsed with petroleum ether and dried overnight at 40°C under reduced pressure.

Yield: 50.94 g (76%) of **2**, brown crystals

5 **3-(4-Pyridinyloxy)phenylamine**



15 a) 200 g (1.44 mol) of 3-nitrophenol and 457.93 g (1.44 mol) of bipyridine were thoroughly mixed and slowly heated to 150°C. After the batch had been stirred at 150°C for 3 hours, it was poured while still hot into 5 l of ice-water. The mixture was acidified using hydrochloric acid, and the aqueous phase was washed 2x with 3 l of methyl tert-butyl ether. The aqueous phase was rendered basic (pH 12) using conc. sodium hydroxide solution and extracted 2x with 3 l of methyl tert-butyl ether. The combined organic phases were washed 4x with 1 l of water, dried over Na₂SO₄, filtered and evaporated. The residue was dissolved in 2 l of diethyl ether, 20 g of activated carbon were added, and the mixture was stirred for 1 hour and filtered. The filtrate was evaporated to about 200 ml, and the product was brought to crystallization in the ice bath by addition of 500 ml of petroleum ether. The crystals were filtered off with suction and dried under reduced pressure.

20

25

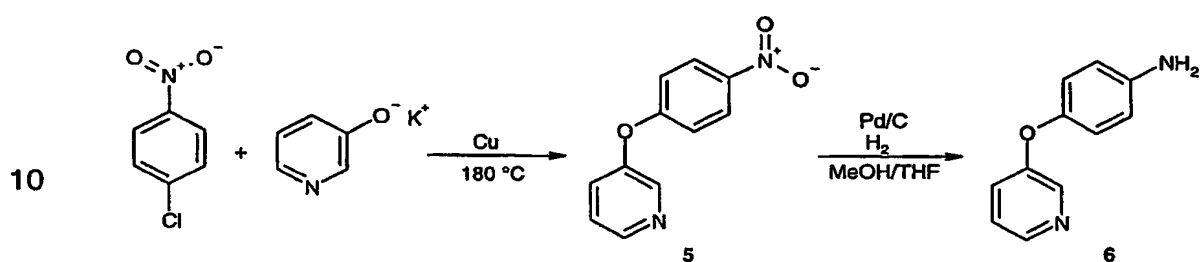
Yield: 131 g (42%) of **3**, beige crystals

30 b) Compound **3** was hydrogenated at room temperature using Pd/C in MeOH. The reaction solution was filtered through kieselguhr and rinsed with MeOH, and the filtrate was subsequently evaporated. The residue

was digested with diethyl ether, filtered off with suction, rinsed with diethyl ether and dried overnight at 40°C under reduced pressure.

Yield: 98.08 g (87%) of 4, pale-brown crystals

5 4-(3-Pyridinyloxy)phenylamine



125 g (0.94 mol) of 3-hydroxypyridine, potassium salt, 300 g of 1-chloro-4-nitrobenzene and 15 g of copper were homogenized and heated to 180°C. The reaction mixture was stirred at 180°C for 6 hours and cooled to 90°C, and methyl tert-butyl ether was subsequently added rapidly. The suspension was stirred for 1 hour and filtered with suction. The filtrate was extracted 3× with 1 l of 10% HCl solution. The aqueous phase was rendered alkaline using NH₄OH solution and extracted with ethyl acetate. The combined organic phases were dried using Na₂SO₄, filtered and evaporated. The residue was purified by column chromatography (1 kg of silica gel, eluent: dichloromethane), taken up in 10% HCl solution and extracted with ethyl acetate. The aqueous phase was rendered alkaline using NH₄OH solution, and the deposited crystals were filtered off with suction, washed with a little cold water and dried in air for 4 days.

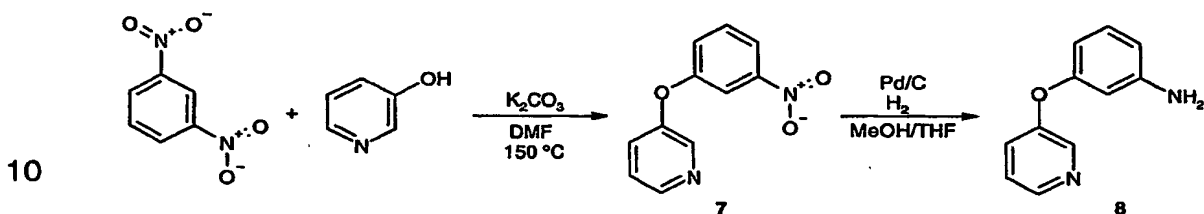
Yield: 44.7 g (22%) of 5, brown crystals

b) Compound **5** was hydrogenated at room temperature using Pd/C in MeOH/THF. The reaction solution was filtered through kieselguhr and rinsed with MeOH, and the filtrate was subsequently evaporated. The

residue was digested with diethyl ether, filtered off with suction, rinsed with diethyl ether and dried overnight at 40°C under reduced pressure.

Yield: 37.14 g (95%) of 6, pale-brown crystals

5 3-(3-Pyridinyloxy)phenylamine



15 a) 50 g (0.53 mol) of 3-hydroxypyridine, 178.8 g (1.05 mol) of 1,3-dinitrobenzene and 159.9 g (1.16 mol) of K_2CO_3 were suspended in 1.4 l of DMF, and the suspension was heated to 150°C. After the reaction mixture had been stirred at 150°C for 16 hours, it was cooled to room temperature and evaporated. The residue was taken up in 1.5 l of ethyl acetate, stirred for 30 minutes and filtered. The filtrate was extracted with 10% HCl solution. The aqueous phase was rendered alkaline using NH_4OH solution and extracted with ethyl acetate. The combined organic phases were dried using Na_2SO_4 , filtered and evaporated. The residue was purified by column chromatography (1 kg of silica gel, eluent: dichloromethane), taken up in 10% HCl solution and extracted with ethyl acetate. The aqueous phase was rendered alkaline using NH_4OH solution and extracted with ethyl acetate. The organic phase was dried using Na_2SO_4 , filtered and evaporated.

25 Yield: 98 g (86%) of 7, brown oil

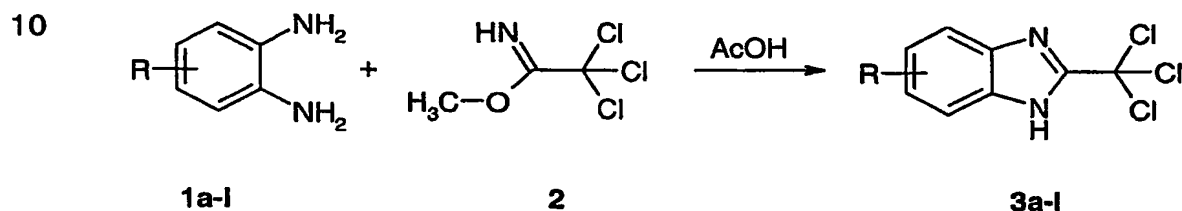
30 b) Compound 7 was hydrogenated at room temperature using Pd/C in MeOH/THF. The reaction solution was filtered through kieselguhr and rinsed with MeOH, and the filtrate was subsequently evaporated. The residue was digested with 50 ml of diethyl ether:petroleum ether = 1:1, filtered off with suction and rinsed with petroleum ether. The mother liquor

was evaporated to dryness, and the residue was stored overnight in the refrigerator. The crystals formed were digested with petroleum ether:diethyl ether = 9:1 and filtered off with suction. The combined crystal batches were dried overnight at 40°C under reduced pressure.

Yield: 77.7 g (91%) of **8**, pale-brown crystals

Synthesis of the benzimidazolecarboxylic acids

Step 1



24.55 mmol of phenylenediamine **1a-k** were dissolved in 50 ml of acetic acid, and 27 mmol of methyl 2,2,2-trichloroacetimidate **2** were added at 0°C over the course of 0.5 hour under an N₂ atmosphere. When the addition was complete, the reaction mixture was slowly warmed to room temperature and stirred at this temperature for 2 hours. The reaction mixture was poured into ice-water, and the resulting precipitate was filtered off with suction, washed with a little water and dried at 40°C under reduced pressure.

- 3a:** R = 5-Cl; brown solid, yield: 82%
- 3b:** R = 5-CF₃; grey-brown solid, yield: 85%
- 3c:** R = 4-CH₃, 5-Cl; pale-brown solid, yield: 83%
- 3d:** R = 4-Br, 6-CF₃; pale-yellow solid, yield: 73%
- 3e:** R = 5-Cl, 6-CF₃; yellow solid, yield: 77%
- 3f:** R = 4-CH₃; pale-yellow solid, yield: 82.5%
- 3g:** R = 4-Cl, 6-CF₃; pale-beige solid, yield: 70.5%
- 3h:** R = 5-Cl, 6-CH₃; beige solid, yield: 96%

3i: R = 4-CF₃, 6-CF₃; pale-beige solid, yield: 47%

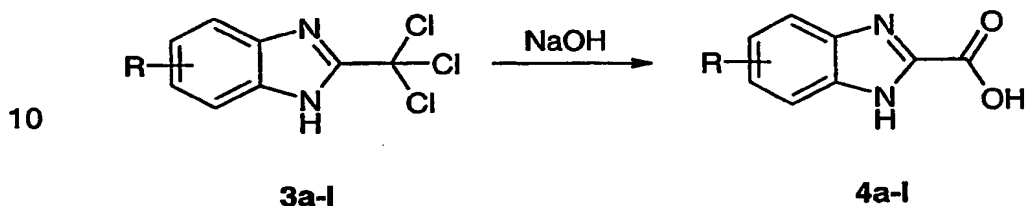
3j: R = 5-Cl, 6-Cl; pale-brown solid, yield: 94.5%

3k: R = 5-CH₃; brown solid, yield: 64%

3l: R = H; commercially available

5

Step 2



15

0.5 g of 2-trichloromethylbenzimidazole **3a-l** was introduced in portions at 0°C into 30 ml of 2N NaOH solution. The resulting solution was acidified (pH 3) using 2N HCl solution and stirred for 1 hour. The mixture was cooled, and the resulting precipitate was filtered off with suction and washed 2 x with water/acetonitrile (3:1) and 2 x with diethyl ether.

20

4a: R = 5-Cl; brown solid, yield: 97%

4b: R = 5-CF₃; pale-red solid, yield: 86%

4c: R = 4-CH₃, 5-Cl; pale-beige solid, yield: 63%

4d: R = 4-Br, 6-CF₃; pale-beige solid, yield: 85%

4e: R = 5-Cl, 6-CF₃; colourless solid, yield: 87%

25

4f: R = 4-CH₃; beige solid, yield: 84%

4g: R = 4-Cl, 6-CF₃; colourless solid, yield: 52.5%

4h: R = 5-Cl, 6-CH₃; yellowish solid, yield: 95%

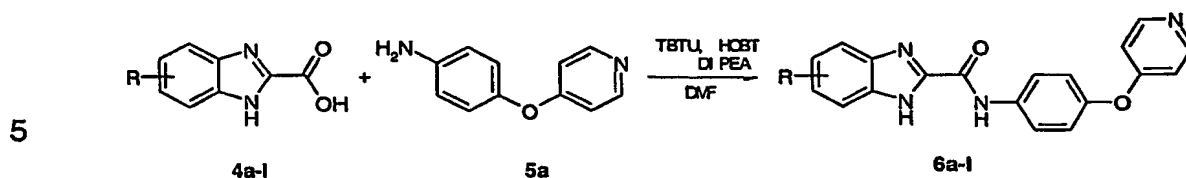
4i: R = 4-CF₃, 6-CF₃; colourless solid, yield: 76%

4j: R = 5-Cl, 6-Cl; beige solid, yield: 100%

30

4k: R = 5-CH₃; pale-brown solid, yield: 48%

4l: R = H; pale-beige solid, yield: 67%

Synthesis of the benzimidazolecarboxamides**N-[4-(pyridin-4-yloxy)phenyl]-5-chloro-1H-benzimidazole-2-carboxamide 6a**

0.064 mmol of benzimidazolecarboxylic acid **4a** was dissolved in DMF together with 0.064 mmol of the amine **5a**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2.5 hours, 0.2 eq. of acid was added, and the mixture was stirred overnight. After a further addition of 0.16 eq. of acid, the reaction mixture was diluted with water after 1.5 hours, and the resulting precipitate was filtered off with suction, washed with water and digested with diethyl ether.

Yield: 75%, pale-brown solid

N-[4-(pyridin-4-yloxy)phenyl]-5-trifluoromethyl-1H-benzimidazole-2-carboxamide 6b

0.064 mmol of benzimidazolecarboxylic acid **4b** was dissolved in DMF together with 0.064 mmol of the amine **5a**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, a further 0.4 eq. of acid was added, and the mixture was stirred for 2 hours. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

Yield: 71.5%, beige solid

N-[4-(pyridin-4-yloxy)phenyl]-5-chloro-4-methyl-1H-benzimidazole-2-carboxamide 6c

0.064 mmol of benzimidazolecarboxylic acid **4c** was dissolved in DMF together with 0.064 mmol of the amine **5a**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, 0.3 eq. of acid was added, and the mixture was stirred for 2 hours. After further addition of 0.3 eq. of acid, the reaction mixture was diluted with water after 2 hours, and the resulting precipitate was filtered off with suction, washed with water and digested with diethyl ether and ethyl acetate.

Yield: 96%, pale-beige solid

N-[4-(pyridin-4-yloxy)phenyl]-4-bromo-6-trifluoromethyl-1H-benzimidazole-2-carboxamide 6d

0.064 mmol of benzimidazolecarboxylic acid **4d** was dissolved in DMF together with 0.064 mmol of the amine **5a**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, a further 0.2 eq. of acid was added, and the mixture was stirred overnight. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

Yield: 68%, pale-beige solid

N-[4-(pyridin-4-yloxy)phenyl]-5-chloro-6-trifluoromethyl-1H-benzimidazole-2-carboxamide 6e

0.064 mmol of benzimidazolecarboxylic acid **4e** was dissolved in DMF together with 0.064 mmol of the amine **5a**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room

temperature. After 2 hours, a further 0.2 eq. of acid was added, and the mixture was stirred for 2 hours. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

5 Yield: 61%, beige solid

N-[4-(pyridin-4-yloxy)phenyl]-4-methyl-1H-benzimidazole-2-carboxamide 6f

10 0.064 mmol of benzimidazolecarboxylic acid **4f** was dissolved in DMF together with 0.064 mmol of the amine **5a**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 3 hours, a further 0.3 eq. of acid was added, and the mixture was stirred overnight. The reaction mixture was diluted with water, 15 and the resulting precipitate was filtered off with suction and washed with water.

Yield: 73%, beige solid

20 **N-[4-(pyridin-4-yloxy)phenyl]-4-chloro-6-trifluoromethyl-1H-benzimidazole-2-carboxamide 6g**

0.064 mmol of benzimidazolecarboxylic acid **4g** was dissolved in DMF together with 0.064 mmol of the amine **5a**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred overnight at 25 room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water. Yield: 65%, pale-beige solid

30 **N-[4-(pyridin-4-yloxy)phenyl]-5-chloro-6-methyl-1H-benzimidazole-2-carboxamide 6h**

0.064 mmol of benzimidazolecarboxylic acid **4h** was dissolved in DMF together with 0.064 mmol of the amine **5a**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water. The resulting solid was digested a number of times with ethyl acetate, and the combined filtrates were evaporated.

Yield: 26%, brown solid

N-[4-(pyridin-4-yloxy)phenyl]-4,6-bis(trifluoromethyl)-1H-benzimidazole-2-carboxamide **6i**

0.064 mmol of benzimidazolecarboxylic acid **4i** was dissolved in DMF together with 0.064 mmol of the amine **5a**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

Yield: 72%, pale-beige solid

N-[4-(pyridin-4-yloxy)phenyl]-5,6-dichloro-1H-benzimidazole-2-carboxamide **6j**

0.064 mmol of benzimidazolecarboxylic acid **4j** was suspended in DMF together with 0.064 mmol of the amine **5a**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

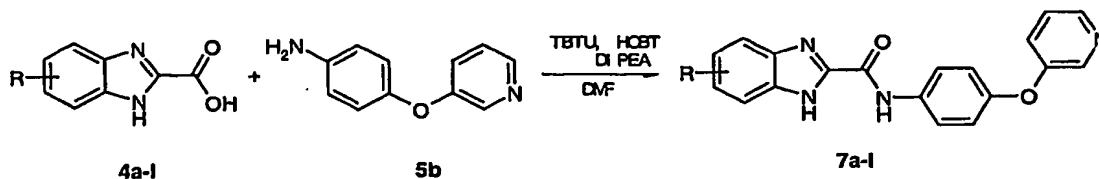
Yield: 51%, pale-brown solid

N-[4-(pyridin-4-yloxy)phenyl]-5-methyl-1H-benzimidazole-2-carboxamide 6k

0.064 mmol of benzimidazolecarboxylic acid **4k** was dissolved in DMF together with 0.064 mmol of the amine **5a**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 4 hours, 0.3 eq. of acid was added, and the mixture was stirred overnight. After further addition of 0.3 eq. of acid, the reaction mixture was diluted with water after 2 hours, and the resulting precipitate was filtered off with suction and washed with water. The resulting crude product was purified by chromatography (ethyl acetate/n-heptane: 9/1). Yield: 39.5%, beige solid

N-[4-(pyridin-4-yloxy)phenyl]-1H-benzimidazole-2-carboxamide 6l

0.064 mmol of benzimidazolecarboxylic acid **4l** was dissolved in DMF together with 0.064 mmol of the amine **5a**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred overnight at room temperature. A further 0.25 eq. of acid was added, and the mixture was stirred for 4 hours. The reaction mixture was diluted with water and extracted a number of times with ethyl acetate. The combined organic phases were washed 2 x with water, dried, filtered and evaporated. Yield: 99%, colourless solid



N-[4-(pyridin-3-yloxy)phenyl]-5-chloro-1H-benzimidazole-2-carboxamide 7a

0.064 mmol of benzimidazolecarboxylic acid **4a** was dissolved in DMF together with 0.064 mmol of the amine **5b**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2.5 hours, 0.2 eq. of acid was added, and the mixture was stirred overnight. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction, washed with water and digested with diethyl ether.

Yield: 69%, pale-brown solid

10

N-[4-(pyridin-3-yloxy)phenyl]-5-trifluoromethyl-1H-benzimidazole-2-carboxamide 7b

0.064 mmol of benzimidazolecarboxylic acid **4b** was dissolved in DMF together with 0.064 mmol of the amine **5b**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, a further 0.4 eq. of acid was added, and the mixture was stirred for 2 hours. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction, washed with water and digested with diethyl ether.

20

Yield: 57%, colourless solid

N-[4-(pyridin-3-yloxy)phenyl]-5-chloro-4-methyl-1H-benzimidazole-2-carboxamide 7c

0.064 mmol of benzimidazolecarboxylic acid **4c** was dissolved in DMF together with 0.064 mmol of the amine **5b**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, a further 0.3 eq. of acid was added, and the mixture was stirred for 2 hours. The reaction mixture was diluted with

30

water, and the resulting precipitate was filtered off with suction, washed with water and digested with diethyl ether and ethyl acetate.

Yield: 95%, yellow solid

5 N-[4-(pyridin-3-yloxy)phenyl]-4-bromo-6-trifluoromethyl-1H-benzimidazole-2-carboxamide 7d

0.064 mmol of benzimidazolecarboxylic acid **4d** was dissolved in DMF together with 0.064 mmol of the amine **5b**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of
10 DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, a further 0.2 eq. of acid was added, and the mixture was stirred for 2 hours. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

15 Yield: 93%, pale-beige solid

N-[4-(pyridin-3-yloxy)phenyl]-5-chloro-6-trifluoromethyl-1H-benzimidazole-2-carboxamide 7e

0.064 mmol of benzimidazolecarboxylic acid **4e** was dissolved in DMF together with 0.064 mmol of the amine **5b**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of
20 DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, a further 0.1 eq. of acid was added, and the mixture was stirred for 2 hours. The reaction mixture was diluted with
25 water, and the resulting precipitate was filtered off with suction and washed with water.

Yield: 75.5%, colourless solid

N-[4-(pyridin-3-yloxy)phenyl]-4-methyl-1H-benzimidazole-2-carboxamide 7f

0.064 mmol of benzimidazolecarboxylic acid **4f** was dissolved in DMF together with 0.064 mmol of the amine **5b**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 3 hours, a further 0.3 eq. of acid was added, and the mixture was stirred for 2 hours. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

Yield: 73.5%, beige solid

N-[4-(pyridin-3-yloxy)phenyl]-4-chloro-6-trifluoromethyl-1H-benzimidazole-2-carboxamide 7g

0.064 mmol of benzimidazolecarboxylic acid **4g** was dissolved in DMF together with 0.064 mmol of the amine **5b**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred for 4 hours at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

Yield: 73%, pale-beige solid

N-[4-(pyridin-3-yloxy)phenyl]-5-chloro-6-methyl-1H-benzimidazole-2-carboxamide 7h

0.064 mmol of benzimidazolecarboxylic acid **4h** was dissolved in DMF together with 0.064 mmol of the amine **5b**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

The resulting solid was digested a number of times with ethyl acetate, and the combined filtrates were evaporated.

Yield: 36%, brown solid

5 **N-[4-(pyridin-3-yloxy)phenyl]-4,6-bis(trifluoromethyl)-1H-benzimidazole-2-carboxamide 7i**

0.064 mmol of benzimidazolecarboxylic acid **4i** was dissolved in DMF together with 0.064 mmol of the amine **5b**, a solution of TBTU

(0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of

10 DIPEA were added successively, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

Yield: 67%, pale-beige solid

15 **N-[4-(pyridin-3-yloxy)phenyl]-5,6-dichloro-1H-benzimidazole-2-carboxamide 7j**

0.064 mmol of benzimidazolecarboxylic acid **4j** was suspended in DMF together with 0.064 mmol of the amine **5b**, a solution of TBTU

(0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of

20 DIPEA were added successively, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

Yield: 46%, pale-brown solid

25 **N-[4-(pyridin-3-yloxy)phenyl]-5-methyl-1H-benzimidazole-2-carboxamide 7k**

0.064 mmol of benzimidazolecarboxylic acid **4k** was dissolved in DMF together with 0.064 mmol of the amine **5b**, a solution of TBTU

(0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of

30 DIPEA were added successively, and the mixture was stirred at room

temperature. After 4 hours, 0.3 eq. of acid was added, and the mixture was

- 124 -

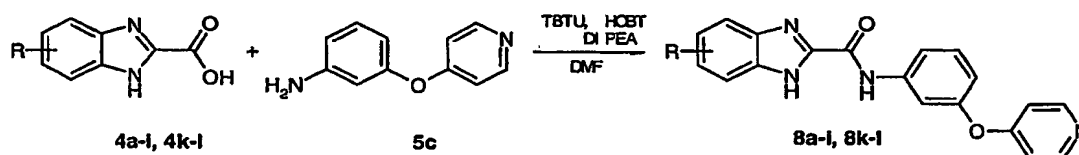
stirred overnight. After further addition of 0.3 eq. of acid, the reaction mixture was diluted with water after 2 hours, and the resulting precipitate was filtered off with suction and washed with water. The resulting crude product was purified by chromatography (ethyl acetate/n-heptane: 6/4).

5 Yield: 57%, pale-orange solid

N-[4-(pyridin-3-yloxy)phenyl]-1H-benzimidazole-2-carboxamide 7l

0.064 mmol of benzimidazolecarboxylic acid 4l was dissolved in DMF together with 0.064 mmol of the amine 5b, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2.5 hours, 0.2 eq. of acid was added, and the mixture was stirred overnight. The reaction mixture was diluted with water and extracted a number of times with ethyl acetate. The combined organic phases were washed 2 x with water, dried, filtered and evaporated.

15 Yield: 92%, pale-beige solid



N-[3-(pyridin-4-yloxy)phenyl]-5-chloro-1H-benzimidazole-2-carboxamide 8a

0.064 mmol of benzimidazolecarboxylic acid 4a was dissolved in DMF together with 0.064 mmol of the amine 5c, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2.5 hours, 0.2 eq. of acid was added, and the mixture was stirred overnight. After further addition of 0.3 eq. of acid, the reaction mixture was diluted with water after 5 hours, and the resulting precipitate

was filtered off with suction, washed with water and digested with diethyl ether.

Yield: 49.5%, pale-brown solid

5 N-[3-(pyridin-4-yloxy)phenyl]-5-trifluoromethyl-1H-benzimidazole-2-carboxamide 8b

0.064 mmol of benzimidazolecarboxylic acid **4b** was dissolved in DMF together with 0.064 mmol of the amine **5c**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of
10 DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, a further 0.4 eq. of acid was added, and the mixture was stirred for 2 hours. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction, washed with water and digested with diethyl ether.

15 Yield: 41%, pink solid

N-[3-(pyridin-4-yloxy)phenyl]-5-chloro-4-methyl-1H-benzimidazole-2-carboxamide 8c

0.064 mmol of benzimidazolecarboxylic acid **4c** was dissolved in DMF
20 together with 0.064 mmol of the amine **5c**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, a further 0.3 eq. of acid was added, and the mixture was stirred for 2 hours. A further 0.3 eq. of acid was added, and
25 the mixture was stirred for 3.5 hours. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction, washed with water and digested with diethyl ether and ethyl acetate.

Yield: 24%, colourless solid

30 N-[3-(pyridin-4-yloxy)phenyl]-4-bromo-6-trifluoromethyl-1H-benzimidazole-2-carboxamide 8d

0.064 mmol of benzimidazolecarboxylic acid **4d** was dissolved in DMF together with 0.064 mmol of the amine **5c**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, a further 0.2 eq. of acid was added, and the mixture was stirred overnight. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

Yield: 25%, pale-beige solid

N-[3-(pyridin-4-yloxy)phenyl]-5-chloro-6-trifluoromethyl-1H-benzimidazole-2-carboxamide 8e

0.064 mmol of benzimidazolecarboxylic acid **4e** was dissolved in DMF together with 0.064 mmol of the amine **5c**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, a further 0.3 eq. of acid was added, and the mixture was stirred overnight. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

Yield: 37%, pale-yellow solid

N-[3-(pyridin-4-yloxy)phenyl]-4-methyl-1H-benzimidazole-2-carboxamide 8f

0.064 mmol of benzimidazolecarboxylic acid **4f** was dissolved in DMF together with 0.064 mmol of the amine **5c**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 3 hours, a further 0.3 eq. of acid was added, and the mixture was stirred overnight. The reaction mixture was diluted with water,

and the resulting precipitate was filtered off with suction and washed with water.

Yield: 46%, yellowish solid

5 **N-[3-(pyridin-4-yloxy)phenyl]-4-chloro-6-trifluoromethyl-1H-benzimidazole-2-carboxamide 8g**

0.064 mmol of benzimidazolecarboxylic acid **4g** was dissolved in DMF together with 0.064 mmol of the amine **5c**, a solution of TBTU

(0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of

10 DIPEA were added successively, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

Yield: 24.5%, colourless solid

15 **N-[3-(pyridin-4-yloxy)phenyl]-5-chloro-6-methyl-1H-benzimidazole-2-carboxamide 8h**

0.064 mmol of benzimidazolecarboxylic acid **4h** was dissolved in DMF together with 0.064 mmol of the amine **5c**, a solution of TBTU

(0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of

20 DIPEA were added successively, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

The resulting solid was digested a number of times with ethyl acetate, and the combined filtrates were evaporated.

25 Yield: 16%, brown solid

N-[3-(pyridin-4-yloxy)phenyl]-4,6-bis(trifluoromethyl)-1H-benzimidazole-2-carboxamide 8i

0.064 mmol of benzimidazolecarboxylic acid **4i** was dissolved in DMF together with 0.064 mmol of the amine **5c**, a solution of TBTU

30 (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of

DIPEA were added successively, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water. Yield: 26%, colourless solid

5

N-[3-(pyridin-4-yloxy)phenyl]-5-methyl-1H-benzimidazole-2-carboxamide 8k

0.064 mmol of benzimidazolecarboxylic acid 4k was dissolved in DMF together with 0.064 mmol of the amine 5c, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 4 hours, 0.3 eq. of acid was added, and the mixture was stirred overnight. After further addition of 0.3 eq. of acid, the reaction mixture was diluted with water after 2 hours, and the resulting precipitate was filtered off with suction and washed with water. The resulting crude product was purified by chromatography (ethyl acetate). Yield: 28%, beige solid

10

15

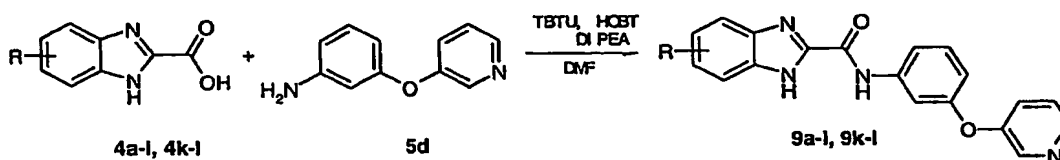
N-[3-(pyridin-4-yloxy)phenyl]-1H-benzimidazole-2-carboxamide 8l

0.064 mmol of benzimidazolecarboxylic acid 4l was dissolved in DMF together with 0.064 mmol of the amine 5c, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2.5 hours, 0.25 eq. of acid was added, and the mixture was stirred overnight. After further addition of 0.5 eq. of acid, the reaction mixture was diluted with water after 16 hours and extracted a number of times with ethyl acetate. The combined organic phases were washed 2 x with water, dried, filtered and evaporated. The residue was digested with ethyl acetate/methanol (a little). Yield: 31%, pale-beige solid

20

25

30



5

N-[3-(pyridin-3-yloxy)phenyl]-5-chloro-1H-benzimidazole-2-carboxamide 9a

0.064 mmol of benzimidazolecarboxylic acid **4a** was dissolved in DMF together with 0.064 mmol of the amine **5d**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2.5 hours, 0.2 eq. of acid was added, and the mixture was stirred overnight. After further addition of 0.2 eq. of acid, the reaction mixture was diluted with water after 1.5 hours, and the resulting precipitate was filtered off with suction, washed with water and digested with diethyl ether.

15

Yield: 34.5%, pale-brown solid

20

N-[3-(pyridin-3-yloxy)phenyl]-5-trifluoromethyl-1H-benzimidazole-2-carboxamide 9b

0.064 mmol of benzimidazolecarboxylic acid **4b** was dissolved in DMF together with 0.064 mmol of the amine **5d**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, a further 0.4 eq. of acid was added, and the mixture was stirred for 2 hours. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction, washed with water and digested with diethyl ether.

25

30

Yield: 57%, pink solid

N-[3-(pyridin-3-yloxy)phenyl]-5-chloro-4-methyl-1H-benzimidazole-2-carboxamide 9c

0.064 mmol of benzimidazolecarboxylic acid **4c** was dissolved in DMF together with 0.064 mmol of the amine **5d**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, a further 0.3 eq. of acid was added, and the mixture was stirred for 2 hours. A further 0.3 eq. of acid was added, and the mixture was stirred for 3.5 hours. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction, washed with water and digested with diethyl ether and ethyl acetate.

Yield: 18%, yellow solid

N-[3-(pyridin-3-yloxy)phenyl]-4-bromo-6-trifluoromethyl-1H-benzimidazole-2-carboxamide 9d

0.064 mmol of benzimidazolecarboxylic acid **4d** was dissolved in DMF together with 0.064 mmol of the amine **5d**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 2 hours, a further 0.2 eq. of acid was added, and the mixture was stirred overnight. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

Yield: 13%, pink solid

N-[3-(pyridin-3-yloxy)phenyl]-5-chloro-6-trifluoromethyl-1H-benzimidazole-2-carboxamide 9e

0.064 mmol of benzimidazolecarboxylic acid **4e** was dissolved in DMF together with 0.064 mmol of the amine **5d**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room

temperature. After 2 hours, a further 0.3 eq. of acid was added, and the mixture was stirred overnight. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

5 Yield: 31%, beige solid

N-[3-(pyridin-3-yloxy)phenyl]-4-methyl-1H-benzimidazole-2-carboxamide 9f

0.064 mmol of benzimidazolecarboxylic acid **4f** was dissolved in DMF together with 0.064 mmol of the amine **5d**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 3 hours, a further 0.3 eq. of acid was added, and the mixture was stirred for 2 hours. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

15 Yield: 56%, beige solid

N-[3-(pyridin-3-yloxy)phenyl]-4-chloro-6-trifluoromethyl-1H-benzimidazole-2-carboxamide 9g

0.064 mmol of benzimidazolecarboxylic acid **4g** was dissolved in DMF together with 0.064 mmol of the amine **5d**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

25 Yield: 19.5%, colourless solid

N-[3-(pyridin-3-yloxy)phenyl]-5-chloro-6-methyl-1H-benzimidazole-2-carboxamide 9h

30

0.064 mmol of benzimidazolecarboxylic acid **4h** was dissolved in DMF together with 0.064 mmol of the amine **5d**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water. The resulting solid was digested a number of times with ethyl acetate, and the combined filtrates were evaporated.

Yield: 16%, brown solid

N-[3-(pyridin-3-yloxy)phenyl]-4,6-bis(trifluoromethyl)-1H-benzimidazole-2-carboxamide 9i

0.064 mmol of benzimidazolecarboxylic acid **4i** was dissolved in DMF together with 0.064 mmol of the amine **5d**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water, and the resulting precipitate was filtered off with suction and washed with water.

Yield: 32%, pale-beige solid

N-[3-(pyridin-3-yloxy)phenyl]-5-methyl-1H-benzimidazole-2-carboxamide 9k

0.064 mmol of benzimidazolecarboxylic acid **4k** was dissolved in DMF together with 0.064 mmol of the amine **5d**, a solution of TBTU (0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of DIPEA were added successively, and the mixture was stirred at room temperature. After 4 hours, 0.3 eq. of acid was added, and the mixture was stirred overnight. After further addition of 0.3 eq. of acid, the reaction mixture was diluted with water after 2 hours, and the resulting precipitate was filtered off with suction and washed with water. The resulting crude product was purified by chromatography (ethyl acetate/n-heptane: 4/6).

Yield: 56%, orange solid

N-[3-(pyridin-3-yloxy)phenyl]-1H-benzimidazole-2-carboxamide 9I

0.064 mmol of benzimidazolecarboxylic acid **4I** was dissolved in DMF
5 together with 0.064 mmol of the amine **5d**, a solution of TBTU
(0.096 mmol) in DMF, HOBT (0.026 mmol) in DMF and 0.32 mmol of
DIPEA were added successively, and the mixture was stirred at room
temperature. After 2.5 hours, 0.2 eq. of acid was added, and the mixture
was stirred overnight. After further addition of 0.2 eq. of acid, the reaction
10 mixture was diluted with water after 3 hours, and the resulting precipitate
was filtered off with suction, washed with water and digested with diethyl
ether.

Yield: 76%, pale-beige solid

15 The compounds (1) to (72) as described above can preferably be
produced according to the procedures described herein or in an analogous
manner thereof.

Example A: Injection vials

20

A solution of 100 g of an active compound of the formula I and 5 g of
disodium hydrogenphosphate is adjusted to pH 6.5 in 3 l of double-distilled
water using 2N hydrochloric acid, sterile-filtered, dispensed into injection
vials, lyophilized under sterile conditions and aseptically sealed. Each
25 injection vial contains 5 mg of active compound.

Example B: Suppositories

A mixture of 20 g of an active compound of the formula I is fused with
100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and
30 allowed to cool. Each suppository contains 20 mg of active compound.

Example C: Solution

5 A solution of 1 g of an active compound of the formula I, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water is prepared. It is adjusted to pH 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

10

500 mg of an active compound of the formula I is mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: Tablets

15

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to give tablets in a customary manner such that each tablet contains 10 mg of active compound.

20

Example F: Coated tablets

25 Analogously to Example E, tablets are pressed and are then coated in a customary manner using a coating of sucrose, potato starch, talc, tragacanth and colourant.

Example G: Capsules

30 2 kg of active compound of the formula I are dispensed into hard gelatin capsules in a customary manner such that each capsule contains 20 mg of the active compound.

Example H: Ampoules

5 A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterile-filtered, dispensed into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

10

15

20

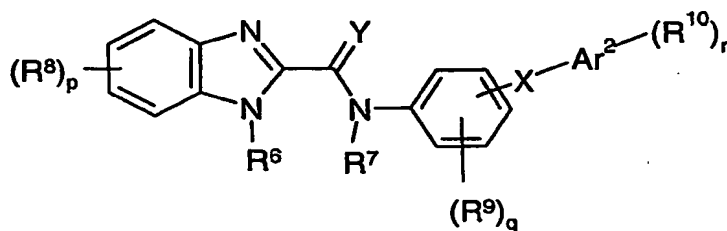
25

30

Claims

1. Benzimidazole carboxamides of formula I

5



10

wherein

R^6, R^7 are independently from one another H, A or SO_2A ,

15

A is independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, alkylencycloalkyl, alkoxy and alkoxyalkyl,

20

R^8, R^9 and R^{10} are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal , $\text{CH}(\text{Hal})_2$, $\text{C}(\text{Hal})_3$, NO_2 , $(\text{CH}_2)_n\text{CN}$, $(\text{CH}_2)_n\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{OR}^{11}$, $(\text{CH}_2)_n\text{O}(\text{CH}_2)_k\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{COOR}^{12}$, $(\text{CH}_2)_n\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{COR}^{13}$, $(\text{CH}_2)_n\text{NR}^{11}\text{CONR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{SO}_2\text{A}$, $(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{S}(\text{O})_u\text{R}^{13}$, $(\text{CH}_2)_n\text{OC}(\text{O})\text{R}^{13}$, $(\text{CH}_2)_n\text{COR}^{13}$, $(\text{CH}_2)_n\text{SR}^{11}$, $\text{CH}=\text{N}-\text{OA}$, $\text{CH}_2\text{CH}=\text{N}-\text{OA}$, $(\text{CH}_2)_n\text{NHOA}$, $(\text{CH}_2)_n\text{CH}=\text{N}-\text{R}^{11}$, $(\text{CH}_2)_n\text{OC}(\text{O})\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{NR}^{11}\text{COOR}^{12}$, $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{CH}_2\text{CH}_2\text{OR}^{13}$, $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{CH}_2\text{CH}_2\text{OCF}_3$, $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{C}(\text{R}^{13})\text{HCOOR}^{12}$, $\text{C}(\text{R}^{13})\text{HCOOR}^{12}$, $(\text{CH}_2)_n\text{N}(\text{R}^{11})\text{CH}_2\text{CH}_2\text{N}(\text{R}^{12})\text{CH}_2\text{COOR}^{12}$,

30

- $(CH_2)_nN(R^{11})CH_2CH_2NR^{11}R^{12}$, $CH=CHCOOR^{11}$,
 $CH=CHCH_2NR^{11}R^{12}$, $CH=CHCH_2NR^{11}R^{12}$,
 $CH=CHCH_2OR^{13}$, $(CH_2)_nN(COOR^{11})COOR^{12}$,
 $(CH_2)_nN(CONH_2)COOR^{11}$, $(CH_2)_nN(CONH_2)CONH_2$,
 $(CH_2)_nN(CH_2COOR^{11})COOR^{12}$,
 $(CH_2)_nN(CH_2CONH_2)COOR^{11}$,
 $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{11}$,
 $(CH_2)_nCHR^{13}COOR^{11}$, $(CH_2)_nCHR^{13}CH_2OR^{14}$,
 $(CH_2)_nOCN$ and $(CH_2)_nNCO$, wherein
- R^{11} , R^{12} are independently selected from a group consisting of
 H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$, or in $NR^{11}R^{12}$,
- R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-,
 6- or 7-membered heterocyclous which optionally
 contains 1 or 2 additional hetero atoms, selected from
 N, O an S,
- R^{13} , R^{14} are independently selected from a group consisting of
 H, Hal, A, $(CH_2)_mAr^4$ and $(CH_2)_mHet$,
- Ar^3 , Ar^4 are independently from one another aromatic
 hydrocarbon residues comprising 5 to 12 and preferably
 5 to 10 carbon atoms which are optionally substituted by
 one or more substituents, selected from a group
 consisting of A, Hal, NO_2 , CN, OR^{15} , $NR^{15}R^{16}$, $COOR^{15}$,
 $CONR^{15}R^{16}$, $NR^{15}COR^{16}$, $NR^{15}CONR^{15}R^{16}$, $NR^{16}SO_2A$,
 COR^{15} , $SO_2R^{15}R^{16}$, $S(O)_uA$ and $OOCR^{15}$,
- Het is a saturated, unsaturated or aromatic heterocyclic
 residue which is optionally substituted by one ore more
 substituents, selected from a group consisting of A, Hal,

NO₂, CN, OR¹⁵, NR¹⁵R¹⁶, COOR¹⁵, CONR¹⁵R¹⁶,
 NR¹⁵COR¹⁶, NR¹⁵CONR¹⁵R¹⁶, NR¹⁶SO₂A, COR¹⁵,
 SO₂R¹⁵R¹⁶, S(O)_nA and OOCR¹⁵,

- 5 R¹⁵, R¹⁶ are independently selected from a group consisting of
 H, A, and (CH₂)_mAr⁶, wherein
- 10 Ar⁶ is a 5- or 6-membered aromatic hydrocarbon which is
 optionally substituted by one or more substituents
 selected from a group consisting of methyl, ethyl, propyl,
 2-propyl, tert.-butyl, Hal, CN, OH, NH₂ and CF₃,
- 15 X represents a bond or is (CR¹¹R¹²)_n, or (CHR¹¹)_n-Q-
 (CHR¹²)_i, wherein
- 20 Q is selected from a group consisting of O, S, N-R¹⁵,
 (CHAl₂)_i, (O-CHR¹⁸)_i, (CHR¹⁸-O)_i, CR¹⁸=CR¹⁹, (O-
 CHR¹⁸CHR¹⁹)_i, (CHR¹⁸CHR¹⁹-O)_i, C=O, C=S, C=NR¹⁵,
 CH(OR¹⁵), C(OR¹⁵)(OR²⁰), C(=O)O, OC(=O), OC(=O)O,
 C(=O)N(R¹⁵), N(R¹⁵)C(=O), OC(=O)N(R¹⁵),
 N(R¹⁵)C(=O)O, CH=N-O, CH=N-NR¹⁵, S=O, SO₂,
 SO₂NR¹⁵ and NR¹⁵SO₂, wherein
- 25 R¹⁸, R¹⁹, R²⁰ are independently selected from the meanings given for
 R⁸, R⁹ and R¹⁰, preferably independently selected from
 the group consisting of H, A, Hal, CH₂Hal, CH(Hal)₂,
 C(Hal)₃, NO₂, (CH₂)_nCN, (CH₂)_nOR¹¹, (CH₂)_nNR¹¹R¹²,
 (CH₂)_nO(CH₂)_kNR¹¹R¹², (CH₂)_nCOOR¹³,
 (CH₂)_nCONR¹¹R¹², (CH₂)_nNR¹¹COR¹³,
 (CH₂)_nNR¹¹CONR¹¹R¹², (CH₂)_nNR¹¹SO₂A,
- 30

- 139 -

$(\text{CH}_2)_n\text{SO}_2\text{NR}^{11}\text{R}^{12}$, $(\text{CH}_2)_n\text{S(O)}_u\text{R}^{13}$, $(\text{CH}_2)_n\text{COR}^{13}$,
 $(\text{CH}_2)_n\text{SR}^{11}$, $(\text{CH}_2)_n\text{NHOA}$ and $(\text{CH}_2)_n\text{NR}^{11}\text{COOR}^{13}$,

- 5 h, i are independently from each other 0, 1, 2, 3, 4, 5, or 6,
 and
- j is 1, 2, 3, 4, 5, or 6,
- 10 Y is selected from O, S, NR^{21} , $\text{C(R}^{22})\text{-NO}_2$, $\text{C(R}^{22})\text{-CN}$ and
 C(CN)_2 , wherein
- R^{21} is independently selected from the meanings given for
 R^{13} , R^{14} and
- 15 R^{22} is independently selected from the meanings given for
 R^{11} , R^{12} ,
- p, r are independently from one another 0, 1, 2, 3, 4 or 5,
- 20 q is 0, 1, 2, 3 or 4, preferably 0, 1 or 2,
- u is 0, 1, 2 or 3, preferably 0, 1 or 2,
- and
- 25 Hal is independently selected from a group consisting of F,
 Cl, Br and I;

30 and the physiologically acceptable derivatives, salts and solvates thereof.

2. Benzimidazole carboxamide according to claim 1, wherein

5	Ar^2	is selected from aromatic hydrocarbons containing 6 to 10 and especially 6 carbon atoms and ethylenical unsaturated or aromatic heterocyclic residues containing 3 to 8 and especially 4 to 6 carbon atoms and one or two heteroatoms, independently selected from N, O and S and especially selected from N and O,
10	R^8, R^9 and R^{10}	are independently selected from a group consisting of H, A, cycloalkyl comprising 3 to 7 carbon atoms, Hal, CH_2Hal , $CH(Hal)_2$, $C(Hal)_3$, NO_2 , $(CH_2)_nCN$, $(CH_2)_nOR^{11}$, $(CH_2)_nNR^{11}R^{12}$, $(CH_2)_nO(CH_2)_kNR^{11}R^{12}$, $(CH_2)_nCOOR^{13}$, $(CH_2)_nCONR^{11}R^{12}$, $(CH_2)_nNR^{11}COR^{13}$, $(CH_2)_nNR^{11}CONR^{11}R^{12}$, $(CH_2)_nNR^{11}SO_2A$, $(CH_2)_nSO_2NR^{11}R^{12}$, $(CH_2)_nS(O)_uR^{13}$, $(CH_2)_nOC(O)R^{13}$, $(CH_2)_nCOR^{13}$, $(CH_2)_nSR^{11}$, $(CH_2)_nNHOA$, $(CH_2)_nNR^{11}COOR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OR^{13}$, $(CH_2)_nN(R^{11})CH_2CH_2OCF_3$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^8$, $(CH_2)_nN(R^{11})C(R^{13})HCOOR^8$, $(CH_2)_nN(COOR^{13})COOR^{14}$, $(CH_2)_nN(CONH_2)COOR^{13}$, $(CH_2)_nN(CONH_2)CONH_2$, $(CH_2)_nN(CH_2COOR^{13})COOR^{14}$, $(CH_2)_nN(CH_2CONH_2)COOR^{13}$, $(CH_2)_nN(CH_2CONH_2)CONH_2$, $(CH_2)_nCHR^{13}COR^{14}$, $(CH_2)_nCHR^{13}COOR^{14}$ and $(CH_2)_nCHR^{13}CH_2OR^{14}$,
25	X	represents a bond or is $(CR^{11}R^{12})_h$, or $(CHR^{11})_h-Q$ or $(CHR^{12})_i$, wherein
30	Q	is selected from a group consisting of O, S, $N-R^{15}$, $(CHal_2)_j$, $(O-CHR^{18})_j$, $(CHR^{18}-O)_j$, $CR^{18}=CR^{19}$, $(O-CHR^{18}CHR^{19})_j$, $(CHR^{18}CHR^{19}-O)_j$, $C=O$, $C=NR^{15}$, $CH(OR^{15})$, $C(OR^{15})(OR^{20})$, $C(=O)N(R^{15})$, $N(R^{15})C(=O)$,

- 141 -

$\text{CH}=\text{N}-\text{NR}^{15}$, $\text{S}=\text{O}$, SO_2 , $\text{SO}_2\text{NR}^{15}$ and $\text{NR}^{15}\text{SO}_2$,
wherein

h, i are independently from each other 0, 1, 2, 3, 4, 5 or 6,
5 preferably 0, 1, 2 or 3 and

j is 1, 2, 3, 4, 5 or 6, preferably 1, 2, 3 or 4,

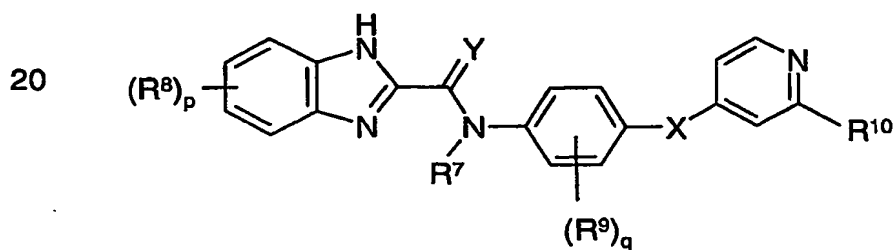
p is 1, 2, 3 or 4, preferably 1, 2 or 3, and

10

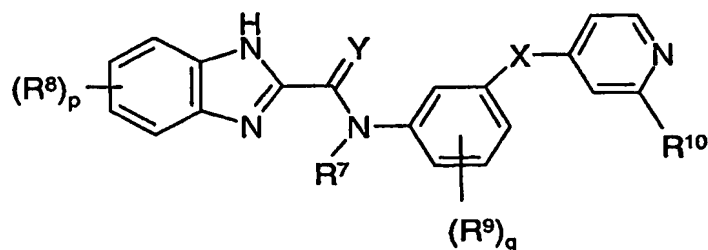
r is 0, 1, 2, or 3, preferably 0, 1 or 2;

and the physiologically acceptable derivatives, salts and solvates thereof.

15 3. Benzimidazole carboxamide according to claim 1 or 2, selected from the compounds of the formulae Ia, Ib, Ic and Id,

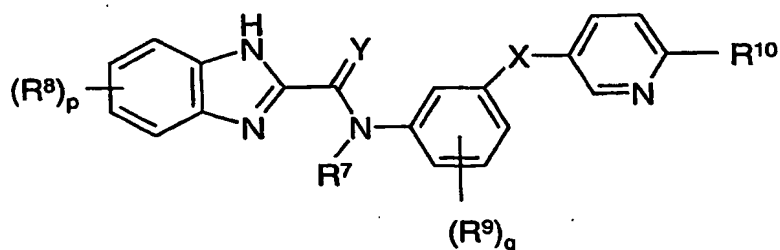


25



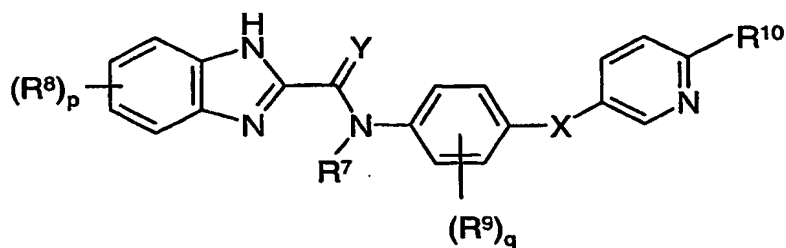
30

- 142 -



Ic

5



Id

10

wherein

15

R^8 , p , X , Y , R^9 and q are as defined in claims 1 or 2, and R^{10} is H or as defined in claims 1 or 2;

and the physiologically acceptable derivatives, salts and solvates thereof.

20

4. Benzimidazole carboxamide according to claim 3, additionally comprising one or two substituents selected from the group consisting of $O(CH_2)_nNR^{11}R^{12}$, $NR^{11}(CH_2)_nNR^{11}R^{12}$, $O(CH_2)_nOR^{12}$ and $NR^{11}(CH_2)_nOR^{12}$,

25

wherein

R^{11} , R^{12} are independently selected from a group consisting of H, A, $(CH_2)_mAr^3$ and $(CH_2)_mHet$, or in $NR^{11}R^{12}$,

R^{11} and R^{12} form, together with the N-atom they are bound to, a 5-, 6- or 7-membered heterocyclous which optionally

30

contains 1 or 2 additional hetero atoms, selected from
N, O and S, and
n is 1, 2, 3, 4, 5 or 6.

- 5 5. Benzimidazole carboxamide according to one of the claims 1 to 4,
selected from the compounds (1) to (72) of table 1.
6. Benzimidazole carboxamide according to one of the claims 1 to 5 as
a medicament.
- 10 7. Benzimidazole carboxamide according to one of the claims 1 to 5 as
a kinase inhibitor.
8. Benzimidazole carboxamide according to claim 7, characterized in
15 that the kinases are selected from raf-kinases.
9. Pharmaceutical composition, characterized in that it contains one or
more compounds according to one of the claims 1 to 5.
- 20 10. Pharmaceutical composition according to claim 9, characterised in
that it contains one or more additional compounds, selected from the
group consisting of physiologically acceptable excipients, auxiliaries,
adjuvants, carriers and pharmaceutical active ingredients other than
the compounds according to one of the claims 1 to 5.
- 25 11. Process for the manufacture of a pharmaceutical composition,
characterised in that one or more compounds according to one of the
claims 1 to 5 and one or more compounds, selected from the group
consisting of carriers, excipients, auxiliaries and pharmaceutical
30 active ingredients other than the compounds according to one of the
claims 1 to 5, is processed by mechanical means into a
pharmaceutical composition that is suitable as dosageform for

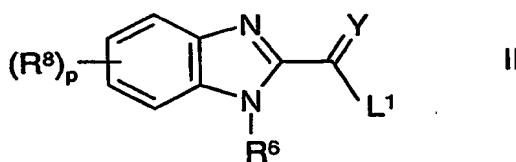
application and/or administration to a patient.

- 5
12. Use of a compound according to one of the claims 1 to 5 as a pharmaceutical.
13. Use of a compound according to one of the claims 1 to 5 in the treatment and/or prophylaxis of disorders.
- 10
14. Use of a compound according to one of the claims 1 to 5 for producing a pharmaceutical composition for the treatment and/or prophylaxis of disorders.
- 15
15. Use according to claim 13 or 14, characterised in that the disorders are caused, mediated and/or propagated by raf-kinases.
16. Use according to claim 13, 14 or 15, characterised in that the disorders are selected from the group consisting of hyperproliferative and nonhyperproliferative disorders.
- 20
17. Use according to claim 13, 14, 15 or 16, characterised in that the disorder is cancer.
18. Use according to claim 13, 14, 15 or 16, characterised in that the disorder is noncancerous.
- 25
19. Use according to claim 13, 14, 15, 16 or 18, characterised in that the noncancerous disorders are selected from the group consisting of infections, psoriasis, arthritis, inflammation, endometriosis, scarring, benign prostatic hyperplasia, immunological diseases, autoimmune diseases and immunodeficiency diseases.
- 30

20. Use according to one of the claims 13 to 17, characterised in that the disorders are selected from the group consisting of brain cancer, lung cancer, squamous cell cancer, bladder cancer, gastric cancer, pancreatic cancer, hepatic cancer, renal cancer, colorectal cancer, breast cancer, head cancer, neck cancer, oesophageal cancer, gynaecological cancer, thyroid cancer, lymphoma, chronic leukaemia and acute leukaemia.
21. Use according to one of the claims 13 to 16, characterised in that the disorders are selected from the group consisting of arthritis, restenosis; fibrotic disorders; mesangial cell proliferative disorders, diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, organ transplant rejection, glomerulopathies, metabolic disorders, inflammation and neurodegenerative diseases.
22. Use of a compound according to one of the claims 1 to 5 as a raf-kinase inhibitor.
23. Use according to claim 22, characterised in that the raf-kinase is selected from the group consisting of A-Raf, B-Raf and c-Raf-1.
24. Method for the treatment and/or prophylaxis of disorders, characterised in that one or more compounds according to one of the claims 1 to 5 is administered to a patient in need of such a treatment.
25. Method according to claim 24, characterised in that the one or more compounds according to one of the claims claim 1 to 5 are administered as a pharmaceutical composition according to claim 9 or 10.

- 146 -

26. Method for the treatment and/or prophylaxis of disorders according to claim 25, characterised in that the disorders are as defined in one of the claims 15 to 21.
- 5 27. Method for the treatment according to claim 26, characterised in that the disorders is cancerous cell growth mediated by raf-kinase.
28. Method for producing compounds of formula I, characterised in that
- 10 a) a compound of formula II

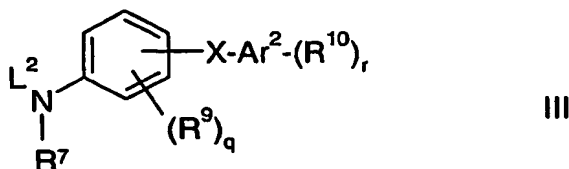


wherein

- 20 L^1 is Cl, Br, I, OH, an esterified OH-group or a diazonium moiety, and R^6 , R^8 , p and Y are as defined in claim 1,

is reacted

- 25 b) with a compound of formula III,



- 147 -

wherein

L^2 is H or a metal ion, and R^7 , R^9 , q , X , Ar^2 , R^{10} and r are as defined in claim 1,

5

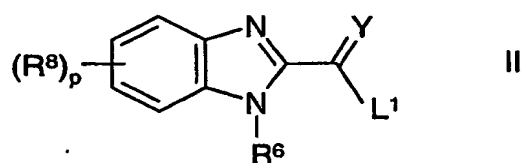
and optionally

c) isolating and/or treating the compound of formula I obtained by said reaction with an acid, to obtain the salt thereof.

10

29. Compound of formula II,

15



20

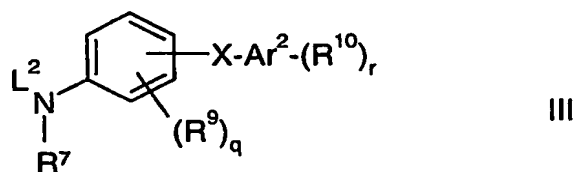
wherein

L^1 is Cl, Br, I, OH, an esterified OH-group or a diazonium moiety, and R^6 , R^8 , p and Y are as defined in claim 1.

25

30. Compound of formula III,

30



wherein

L^2 is H or a metal ion, and R^7 , R^9 , q, X, Ar^2 , R^{10} and r are as
defined in claim 1.

5

10

15

20

25

30

- 149 -

Abstract

The present invention relates to benzimidazole carboxamides of formula I,
the use of the compounds of formula I as inhibitors of raf-kinase, the use
5 of the compounds of formula I for the manufacture of a pharmaceutical
composition and a method of treatment, comprising administering said
pharmaceutical composition to a patient.

10

15

20

25

30

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

{